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Self-Assembled Polymeric Pyridine Copper Catalysts for Huisgen Cycloaddition with Alkynes and Acetylene Gas: Application in Synthesis of Tazobactam

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S Supporting Information

ABSTRACT: Novel convoluted polymeric pyridine copper(I) catalysts PVPy-Cu were developed for the Huisgen cyclization of organic azides using alkynes and acetylene gas. They were readily prepared based on our molecular convolution of $CuSO_4$. 5H₂O and poly(4-vinylpyridine) (PVPy) in the presence of sodium ascorbate with and without various sodium salts in water. Their structural investigation was conducted using XANES and EXAFS, as well as DFT calculation. The Huisgen cycloaddition of a variety of alkynes and acetylene gas was carried out using 100 to 800 mol ppm of Cu of PVPy-Cu in water, whose turnover numbers reached up to 10 000. This catalytic system was applied to the synthesis of tazobactam, which is an inhibitor of bacterial β -lactamases.

KEYWORDS: polymer, copper, Huisgen cycloaddition, acetylene gas, tazobactam

INTRODUCTION

Huisgen 1,3-dipolar azide-alkyne cycloaddition¹ is an important reaction in click chemistry² and is applied to the preparation of biologically active compounds and biomolecules toward preclinical and clinical applications.³ Meldal and coauthors⁴ and Sharpless and coauthors⁵ independently reported the copper-catalyzed azide-alkyne cycloadditions (CuAAC), in which a Cu(I) catalyst promotes the reaction regioselectively to afford 1,4-substituted 1,2,3-triazols. For application of this catalytic reaction to chemical processes, the development of a heterogeneous catalytic system has been considered a suitable chemical process to prevent the contamination of products through the residues of toxic copper, ligands, and organic solvents as well as to recover and reuse the catalysts in an efficient manner.^{6–9} In particular, the utilization of water as a solvent is also important in terms of sustainable chemical processes using heterogeneous catalysts toward the goal of sustainable development.^{7,9} For this purpose, we developed a reusable amphiphilic self-assembled poly(Nisopropylacrylamide-co-N-vinylimidazole) copper catalyst (MPPI-Cu).¹⁰ MPPI-Cu with 4.5 mol ppm (0.00045 mol %) of Cu promoted CuAAC in t-BuOH/water, whereas the reaction in water was sluggish. We have reported that copper polymericmembrane-installed microflow catalytic reactors drive the Huisgen 1,3-dipolar cycloaddition under flow conditions.¹¹ Our mission is to develop highly active and reusable polymeric copper catalysts that work in water at the mol ppm of Cu level. Here, we report the development of novel molecular convoluted poly(4-vinylpyridine) copper(I) catalysts with various PVPy-Cu bearing anions that promote the Huisgen cycloaddition of a variety of organic azides with alkynes as well as acetylene gas in water at the mol ppm of Cu level. Structural elucidation of the

catalysts was also conducted to show the local structure near the Cu atoms.

RESULTS AND DISCUSSION

In the course of developing polymeric Cu membrane-installed microreactors, we found that anions in the catalytic membrane have a significant role in facilitating the Huisgen cycloaddition.¹¹ In accordance with our previous findings, poly(4-vinylpyridine) copper catalysts PVPy-Cu (3) including a variety of anions were prepared as follows (Scheme 1): The molecular convolution of poly(4-vinylpyridine) (1; 2 mol equiv N) and $CuSO_4 \cdot 5H_2O$ (2; 1 mol equiv Cu) was carried out using a 1.1 mol equivalent of sodium ascorbate in MeOH/H₂O (1:1) at 25 °C for 10 min to provide PVPy-Cu+-SO₄²⁻ (3a) at a 59 wt % yield as an insoluble powder. An SEM image showed that a porous structure occurred on the surface of 3a (Figure 1), and a BET analysis indicated that the specific surface area of 3a was 58 m² g⁻¹. The molecular convolution of 1 and 2 was performed without the use of sodium ascorbate under otherwise similar conditions to afford PVPy- $Cu^{2+}-SO_4^{2-}$ (3b) at a 60 wt % yield. A structural investigation of 3a and 3b was conducted using XANES, EXAFS, and DFT calculations (for details, see the Supporting Information). The results suggest that the local structures of 3a and 3b near Cu atoms are a SO42-bridged dinuclear Cu complex with four pyridines (Scheme 1 (1)) and mononuclear Cu pyridine complexes (Scheme 1 (2)), respectively. Other polymeric pyridine copper catalysts 3c-3h were also prepared from 1 and 2 with various sodium salts (NaX) in the presence of sodium

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Scheme 1. Preparation of PVPy-Cu-X Catalyst 3a, 3b







Figure 1. SEM image of 3a.

ascorbate at a 62%-92 wt % yield (Table 1 and Supporting Information). Copper loading in all catalysts 3a-3h was determined through an ICP-MS analysis, although the structure of 3c-3h was not determined.

Since a variety of polymeric Cu catalysts PVPy-Cu were prepared, their catalytic activity was investigated through a Huisgen cycloaddition reaction of less reactive aliphatic decyl azide (4a) and phenylacetylene (5a) in water (Table 2). When the reaction was conducted in the presence of 0.01 mol % (100 mol ppm) Cu of PVPy-Cu⁺SO₄²⁻ (3a) in water at 65 °C for 16 h, we were pleased to find that the cycloaddition proceeded smoothly, providing the corresponding 1,2,3-triazole 6aa at a 87% yield (entry 1). When the Cu(II) catalyst PVPy-Cu²⁺SO₄²⁻ (3b) was used, a 42% yield of 6aa was given (entry 2). Other

Table 1. Preparation of PVPy-Cu-X Catalyst 3c-3h

PV (2 m	Py (1) + CuSO ₄ (2) ⁻ iol equiv)	NaX (5 mol equiv) sodium ascorbate (50 mol equiv) H ₂ O/MeOH (1:1) rt, 1 h	3c-3h
entry	NaX	catalyst 3	yield (wt %)
1	NaCl	$PVPy-Cu^{+}-Cl^{-}(3c)$	62
2	NaOTf	PVPy-Cu ⁺ -OTf ⁻ (3d)	76
3	HCO ₂ Na	$\frac{\text{PVPy-Cu}^{+}\text{-HCO}_{2}^{-}}{(3e)}$	87
4	NaPSS (sodium poly(4 styrenesulfonate))	• PVPy-Cu ⁺ -PSS ⁻ (3f)	92
5	NaHCO ₃	PVPy-Cu ⁺ -HCO ₃ ⁻ (3g)	83
6	none	PVPy-Cu ⁺ -Asc ⁻ (3h)	79

PVPy-Cu(I) catalysts, prepared from sodium salts of chloride (3c), trifluoromethanesulfonate (3d), formate (3e), poly(4-styrenesulfonate) (3f), bicarbonate (3g), or ascorbate (3h), afforded **6aa** at a 64%–82% yield (entries 3–8). Our previous catalyst MPPI-Cu¹⁰ gave **6aa** at a 56% yield (entry 9).

The Huisgen cycloaddition of a variety of organic azides 4 (2 mmol) and phenylacetylene **5a** (2 mmol) was carried out using 100 mol ppm of Cu (100 mol ppm = 0.07 mg) of PVPy-Cu⁺-SO₄²⁻ (**3a**) and 10 mol % of sodium ascorbate in water (0.5 mL) for 16 h (Table 3). Thus, the reaction of decyl azide (**4a**) and phenylacetylene (**5a**) was carried out at 70 °C to provide the corresponding 1,2,3-triazole **6aa** at a 92% yield (entry 1). The recyclability of the catalyst was investigated under the cycloaddition of benzyl azide (**4b**; 2 mmol) and **5a** (2 mmol) with 0.2 mol % (1.4 mg) of **3a**. The reaction proceeded

Table 2. Comparison of Catalytic Activity in CuAAC of DecylAzide (4a) and Phenylacetylene $(5a)^a$

		Cu catalyst (100 mol ppm Cu) sodium ascorbate (10 mol%)	
nC_9H_{19} N ₃ +	──Ph	H ₂ O	· //C9H19 \(
4 a	5a	65 °C, 16 h	6aa ^{`Ph}
entry		PVPy-Cu ^{<i>m</i>+} -X ^{<i>n</i>-}	yield (%)
1	Р	$VPy-Cu^{+}-SO_{4}^{2-}$ (3a)	87
2	Р	$VPy-Cu^{2+}-SO_{4}^{2-}(3b)$	42
3	Р	$VPy-Cu^+-Cl^-(3c)$	75
4	Р	$VPy-Cu^+-OTf^-(3d)$	64
5	Р	$VPy-Cu^{+}-HCO_{2}^{-}(3e)$	65
6	Р	VPy-Cu ⁺ -PSS ⁻ (3f)	66
7	Р	VPy-Cu ⁺ -HCO ₃ ⁻ (3g)	69
8	Р	VPy-Cu ⁺ -Asc ⁻ (3h)	82
9	Ν	IPPI-Cu	56
aConditions.	1 (20 m	(mal) 5. (2.0 (mal) 2.(0.0002 mm al (Cu)

^aConditions: 4 (2.0 mmol), **5a** (2.0 mmol), **3** (0.0002 mmol Cu), sodium ascorbate (0.20 mmol), and water (0.5 mL).

smoothly, providing the product **6ba** at a 99% yield (entry 2). The insoluble **3a** was readily recovered and reused under similar conditions to give **6ba** at 99% and 92% yields in the second and third uses of the catalyst, respectively (entry 2). Substituted benzylic azides were also suitable substrates to afford **6ca**–**6ja** at a 91%–99% yield (entries 3–10). When functional materials 11-azido-3,6,9-trioxaundecan-1-amine (**4k**) and 2-azidoethyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (**41**) were applied to this catalytic system, the corresponding 1,2,3-triazoles **6ka**

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and **6la** were obtained at 88% and 95% yields, respectively (entries 11 and 12).

The catalytic system was applicable to the reaction of 10 g scales of 4b and 5a (Scheme 2). The reaction of 4b (10 g, 75

Scheme 2. Large-Scale Reactions of 4b (10 g) and 5a (7.5 g)

			PVPy-Cu ⁺ -SO4 ²⁻ (3a) (2.6 mg; 100 mol ppm)	N
Ph N ₃	+	──Ph ·	sodium ascorbate (1.5 g; 7.5 mmol)	Ph N N
4b (10 g; 75 mmo	ol) (7.	5a 5 g; 75 mmo	H ₂ O (20 mL) 50 °C, 16 h I)	`Ph 6ba (17.5 g; 99%)

mmol) with 5a (7.5 g, 75 mmol) was carried out using 3a (2.6 mg) and sodium ascorbate (1.5 g) in water at 50 °C for 16 h to provide the triazoles **6ba** at 17.5 g (99% yield), where recrystallization without column chromatography was conducted for purification of **6ba**. The catalyst **3a** was recovered quantitatively using filtration (2.6 mg).

The Huisgen cycloaddition of benzyl azide (4b) and various terminal alkynes 5 was carried out under similar conditions (Table 4). Arylacetylenes 5b-5d reacted with 4b at 50–70 °C to provide the corresponding products 6bb-6db at a 96%–98% yield (entries 1–3). An aliphatic alkyne 5e and aliphatic alkynes bearing hydroxyl or phenyl groups 5f and 5g were readily converted into the corresponding triazoles at a 92%–98% yield (entries 4–6). A biologically active compound ethynylestradiol (5h) was also applied to this catalytic system, affording the corresponding 1,2,3-triazole 6bh at a 97% yield (entry 7).

Table 3. CuAAC of Organic Azides 4 and Phenylacetylene $(5a)^{a}$

	PVPy-Cu ⁺ -SO ₄ ²⁻ (3	a) (100 mol ppi	m Cu)	N ^N N
R	[∧] N ₃ + ≡−Ph <u>sodium ascor</u>	bate (10 mol%)		<u>_</u> (
	4 5 a 1	1 ₂ O 6 h		e ^{`Ph}
(1 m	ol equiv) (1 mol equiv)	• • •		•
		4 (8C)	6	
entry	4	temp (°C)	0	yield (%)
1	4a (C10H21N3)	70	6aa	92
2ª	4b (PhCH ₂ N ₃)	50	6ba	99 (1st use) 99 (2nd use) 92 (3rd use)
3	4c (4-MeC ₆ H ₄ CH ₂ N ₃)	70	6ca	99
4	4d (2-MeC ₆ H ₄ CH ₂ N ₃)	70	6da	93
5	4e (4-MeOC ₆ H ₄ CH ₂ N ₃)	80	6ea	91
6	4f (4-FC ₆ H ₄ CH ₂ N ₃)	80	6fa	97
7	4g (4- F ₃ CC ₆ H ₄ CH ₂ N ₃)	80	6ga	99
8	4h (4- O ₂ NC ₆ H ₄ CH ₂ N ₃)	80	6ha	99
9	4i (4-NCC ₆ H ₄ CH ₂ N ₃)	80	6ia	99
10	4j (2-C ₁₀ H ₇ CH ₂ N ₃)	80	6ja	94
11	H ₂ N~0~0~N ₃ 4k	80	6ka	88
12	AcO AcO OAc N ₃ 41	80	6la	95

^aConditions: 4 (2.0 mmol), 5a (2.0 mmol), 3a (0.002 mmol), sodium ascorbate (0.20 mmol), water (0.5 mL), and (entry 2) 3a (0.004 mmol).



Ph	PVPy-Cu ⁺ . N ₃ + <u></u> R <u>sodium</u> 5 quiv) (1 mol equiv)	SO ₄ ²⁻ (3a) (100 mo a ascorbate (10 mol H ₂ O (0.5 mL) 16 h	l ppm) <u>%)</u> Ph \6	N _. N ≕∕R
entry	5 (R)	temp (°C)	6	yield (%)
1	5b (4-MeC ₆ H ₄)	50	6bb	98
2	5c (4-MeOC ₆ H ₄)	70	6bc	96
3	5d (4-BuC ₆ H ₄)	70	6bd	97
4	5e (C ₅ H ₁₁)	80	6be	98
5	5f (HO(CH ₂) ₈)	80	6bf	92
6	5g (PhCH ₂ CH ₂)	80	6bg	96
7	HO Sh	80	6bh	97

^aConditions: 4a (2.0 mmol), 5 (2.0 mmol), 3a (0.0002 mmol), sodium ascorbate (0.20 mmol), and water (0.5 mL).

The Huisgen cycloaddition with acetylene gas in water was investigated (Table 5). We previously reported the MPPI-Cu-

Table 5. CuAAC of Organic Azides 4 and Acetylene Gas 7^a

$R ^{N_3} + \equiv$ 4 7 (2 mmol) (in a ballor	PVPy-Cu ⁺ -SO4 ²⁻ (3a) (800 mc sodium ascorbate (50 m H ₂ O (5 mL) 90 °C, 16 h	ol ppm Cu) nol%) 🖕	R N N 8
entry	4	8	yield (%)
1	4b (PhCH ₂ N ₃)	8b	92
2 (no catalyst)	4b	8b	11
3	$4c (4-MeC_6H_4CH_2N_3)$	8c	99
4	4d (2-MeC ₆ H ₄ CH ₂ N ₃)	8d	81
5	$4e (4-MeOC_6H_4CH_2N_3)$	8e	95
6	$4f (4-FC_6H_4CH_2N_3)$	8f	99
7	$4g (4 - F_3 CC_6 H_4 CH_2 N_3)$	8g	94
8	$4h (4- O_2NC_6H_4CH_2N_3)$	8h	99
9	$4i (4-NCC_6H_4CH_2N_3)$	8i	99
10	$4j (2-C_{10}H_7CH_2N_3)$	8j	99
11	$4a (C_{10}H_{21}N_3)$	8a	51
	1) - (1 1 1		1)

^{*a*}Conditions: 4 (2.0 mmol), 7 (in a balloon), 3a (0.0016 mmol), sodium ascorbate (1.0 mmol), water (5 mL), (entry 2) without a catalyst, and (entry 11) in MIBK as a solvent and without the addition of sodium ascorbate.

catalyzed Huisgen cycloaddition with acetylene gas, where the polymeric moiety in MPPI-Cu could stabilize the resulting copper acetylide as a massive protective matrix, and thus monosubstituted 1,2,3-triazoles should be readily and safely prepared.^{10b} However, MPPI-Cu did not efficiently promote the cycloaddition in water. The reaction of benzyl azide (**4b**) with acetylene gas (7; 1 atm, in a balloon) was carried out using **3a** in water at 90 °C for 16 h to provide 1-phenylmethyl-1*H*-1,2,3-triazole (**8b**) at a 92% yield (entry 1), whereas only 11% of the product was obtained without a catalyst (entry 2). The substituted benzylic azides were also shown to be suitable

substrates: The benzylic azides bearing electron-donating groups 4c-4e were readily converted into the corresponding triazoles 8c-8e at a 81%-99% yield (entries 3-5). Benzylic azides bearing electron-withdrawing groups 4f-4i provided the corresponding products 8f-8i at a 94%-99% yield (entries 6-9). 2-Naphthylmethyl azide (4j) led to a cycloaddition affording a 99% yield of the product 8j (entry 10). Although water was not an appropriate solvent in the reaction of aliphatic azide 4a, the reaction in methyl isobutyl ketone (MIBK) provided the product 8a at a 51% yield (entry 11).

 $PVPy-Cu^+-SO_4^{2-}$ (3a) was successfully applied to the synthesis of tazobactam, a pharmaceutical compound of a bacterial β -lactamase inhibitor under atmospheric pressure acetylene gas conditions. There have been several reports on the synthesis of tazobactam using the Huisgen cycloaddition of azide precursors with acetylene gas under high-pressure acetylene gas conditions, although the key cycloaddition under atmospheric pressure conditions has not yet been reported to the best of our knowledge.¹² The cycloaddition of the synthetic intermediate 9^{13} with acetylene gas 7 (1 atm) was carried out in water, and the decomposition of 9 was observed. Finally, the reaction in MIBK without the addition of sodium ascorbate provided protected tazobactam 10 at a 91% yield, whereas larger amounts of **3a** were necessary to efficiently promote the reaction (Scheme 3). An ICP-MS analysis indicated that contamination of copper in 10 was less than 1 ppm (0.35 ppm), which is suitable for the regulations in permitted daily exposure (PDE) of the "Guideline for Elemental Impurities Q3D" by the ICH.¹⁴ In contrast, the reaction with CuI (10 mol %) under similar conditions gave 10 in 26% yield. The cleavage of the protecting group in *m*-cresol¹⁵ afforded tazobactam 11 at a 91% yield under a temperature of 50 °C.

CONCLUSION

In conclusion, we developed a novel highly active self-assembled polymeric copper catalyst PVPy-Cu⁺-SO₄²⁻ (3a) bearing a sulfate anion. It was applied to the Huisgen cycloaddition of various organic azides and terminal alkynes, as well as acetylene

Scheme 3. Synthesis of Tazobactam



gas (1 atm), in water to provide the corresponding mono- or disubstituted 1,2,3-triazoles at up to a quantitative yield. A bioconjugated material and medical compound were also applied to the cycloaddition using this catalytic system. PVPy-Cu⁺-SO₄²⁻ (**3a**) was applied to the synthesis of tazobactam using the Huisgen cycloaddition with acetylene gas at atmospheric pressure.

EXPERIMENTAL SECTION

Preparation of PVPy-Cu⁺-SO₄²⁻ (**3a**). To a methanol solution (20 mL) of poly(4-vinylpyridiene) (210.8 mg, 2.0 mmol) was added an aqueous solution (15 mL) of sodium ascorbate (217.9 mg, 1.1 mmol) and an aqueous solution (5 mL) of CuSO₄·SH₂O (249.7 mg, 1 mmol), successively. The combined mixture was stirred for 10 min at 25 °C to provide light-green precipitates. The precipitates were filtered using a paper filter, and the resulting solid material was washed with Milli-Q water (3 × 30 mL) and methanol (3 × 30 mL) and was dried in vacuo to provide PVPy-Cu⁺-SO₄²⁻ (**3a**) as a light-green p o w d e r (2 7 0 . 1 mg). A n a l. C a l c d f o r $[(C_7H_7N)_{4.05}(Cu^+)_{2.19}(SO_4^{2-})_{1.00}(H_2O)_{3.80}(C_6H_7O_6^{-})_{0.19}]_n$: C, 46.44%; H, 4.93%; N, 7.44%; S, 4.20%; Cu, 18.24%. Found: C, 46.31%; H, 4.95%; N, 7.62%; S, 4.21%; Cu, 18.31%.

General Procedure for the Huisgen Cycloaddition of Organic Azides with Terminal Acetylenes. Water (0.5 mL) was added to a 4 mL vial containing 3a (0.07 mg, 100 mol ppm of Cu), organic azide 4 (2.0 mmol), acetylene 5 (2.0 mmol), and sodium ascorbate (39.6 mg, 0.20 mmol). The resulting mixture was mixed with a reaction mixer at 50-80 °C for 16 h. After cooling to 25 °C, the reaction mixture was extracted with EtOAc, and the resulting organic layer was passed through silica gel column chromatography (eluent, EtOAc/hexane (1:2)). The organic solvent was evaporated to afford triazole 6.

Synthesis of (2S,3S,5R) 3-Methyl-7-oxo-3-(1H-1,2,3triazol-1-yl-methyl)-4-thia-1-azabicyclo[3.2.0]heptane2-carboxylic Acid 4,4-Dioxide,diphenyl Methyl Ester (10). MIBK (0.5 mL) was added to the Schlenk tube containing 3a (8.4 mg, 10 mol % Cu) and azide 9 (110 mg, 0.25 mmol) with a balloon filled with acetylene gas. The reaction mixture was stirred at 90 °C for 24 h. After cooling to 25 °C, the reaction mixture was extracted using EtOAc, and the resulting organic layer was passed through silica gel column chromatography (eluent, EtOAc/hexane (1:1)). Evaporation and recrystallization of the resulting crystal with dichrolomethane and EtOAc afforded 10 as a white crystal (106 mg, 91%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00429.

Procedure for preparation of catalysts, the general procedure for the Huisgen cycloaddition, XAFS analyses and DFT calculation data for structural determination of **3a**, ¹H and ¹³C NMR data, and charts of the products (PDF)

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Notes

The authors declare no competing financial interest.

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