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Metal-Free Fast Azidation Using Tetrabutylammonium Azide: Effective Synthesis of Alkyl Azides and Well-defined Azido-end Polymethacrylates

Chen-Gang Wang, Amerlyn Ming Liing Chong, Yunpeng Lu, Xu Liu and Atsushi Goto*

Abstract: An effective method to synthesize azido-end polymethacrylates using tetrabutylammonium azide (BNN_3) in a non-polar solvent (toluene) was developed. Several low-mass alkyl halides were reacted with BNN_3 in toluene as model reactions and the rate constants of these reactions were determined, confirming fast BNN_3-azidation for tertiary and secondary halides. The end-group transformation of halide-end polymethacrylates was effective and nearly quantitative. Notably, the combination of organocatalyzed living (or reversible deactivation) radical polymerization and BNN_3-azidation enabled metal-free synthesis of azido-end polymethacrylates, including single-azido-end and multi-azido-end functional homopolymers and block copolymer. The rapid and quantitative reaction without using a large excess of BNN_3 metal-free and polar-solvent-free nature, and broad polymer scope are attractive feature of this azidation.

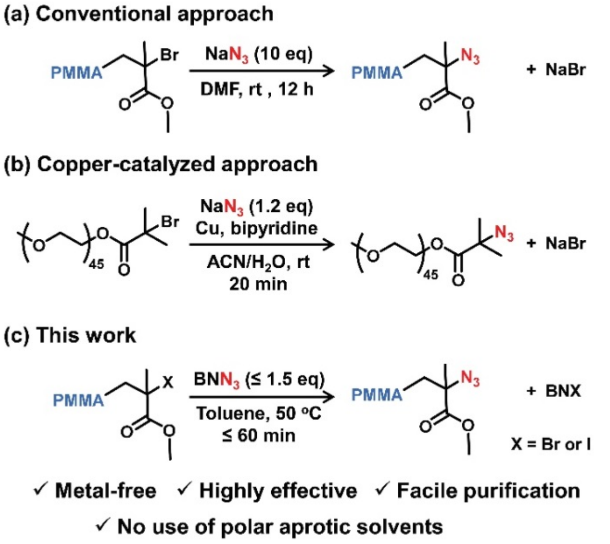
Introduction

Alkyl azides are important precursors in organic chemistry, *e.g.*, in the synthesis of heterocycles, functional peptides, and biomedical molecules.[1–3] Because of the high reactivity, azide chemistry is also extensively utilized in polymer chemistry. Azido-chain-end functionalized polymers are enabling building blocks to construct structurally complex macromolecules *via* 1,3-dipolar cycloadditions, particularly copper(I)-catalyzed azide-alkyne "click" cycloaddition (CuAAC).[4–8]

Sodium azide (NaN_3) is widely used as an azidation agent of alkyl halides and halide-end polymers in polar solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO). Azido-end polystyrenes and polyacrylates were thereby efficiently synthesized. However, the NaN_3-azidation was relatively slow for polymethacrylates because of the difficulty of SN_2 displacement for generating tertiary alkyl azides.[9,10] A 10-fold excess of NaN_3 with long reaction time (≥ 12 h) was generally required for quantitative azidation of bromo-end polymethacrylates due to the tertiary alkyl chain end (Scheme 1a).[11] Because of its explosive nature, the use of a large excess of NaN_3 poses a potential safety concern in a scale-up synthesis. Besides this conventional NaN_3-azidation, Vermonden and coworkers reported a fast NaN_3-azidation using a copper catalyst, attaining a quantitative conversion of a tertiary alkyl bromide in 20 min with 1.2 equivalence of NaN_3 (Scheme 1b).[12] However, the use of copper brings about time-consuming post-purification steps and limits the biomedical and other applications. Han and Tsarevsky generated azide radicals using hypervalent iodine compounds and used the azide radicals to initiate and terminate conventional radical polymerizations.[13] This method elegantly yielded azido-end polymethacrylates in a metal-free manner, while the polymer structures were not aimed to control because of conventional radical polymerization.

Our research group has synthesized iodo-end polymers (polymer–I) *via* reversible complexation mediated polymerization (RCMP), which is an organocatalyzed living (or reversible deactivation) radical polymerization. RCMP uses an alkyl iodide as an initiator and an organic molecule as a catalyst.[14–18] The weak C–I bond at the polymer–I chain-end facilitates end-group modification.[19,20] We recently successfully converted polymethacrylate–I to azido-end polymethacrylate–N_3 using only a small excess of NaN_3 (1.1 eq) in a polar solvent (DMF).[21] The use of iodide instead of bromide enabled the reduction of NaN_3 (1.1 eq (I) vs 10 eq (Br)).

A metallic azide salt NaN_3 is soluble only in polar solvents. In sharp contrast, tetrabutylammonium azide (BNN_3), which is an organic azide salt, is soluble in both polar and nonpolar solvents. In the present work, we used BNN_3 as an azidation reagent in a nonpolar solvent, *i.e.*, toluene (Scheme 1c). BNN_3 was successfully used to initiate anionic polymerization of oxiranes and vinyl monomers to give polymers with an azido group at the initiating chain end.[22,23] However, the stringent moisture-free condition required in anionic polymerizations limits the synthetic accessibility.



Scheme 1. Azidation of Polymethacrylates: (a) Conventional Approach, (b) Copper-catalyzed Approach, and (c) This Work.

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A significant finding in the present work was that the BNN_3-azidation in toluene was as efficient as the conventional NaN_3-azidation in polar solvents. The BNN_3-azidation was rapid and quantitative without using a large excess of BNN_3, metallic catalysts, or polar solvents. We systematically studied the BNN_3-azidation using different alkyl halides (I, Br and Cl) at different temperatures in low-mass systems. We also experimentally determined the azidation rate constant in several systems. We subsequently applied the BNN_3-azidation to polymer systems. We synthesized iodo-end polymethacrylates *via* RCMP and converted them to the azido-end polymethacrylates. The combination of RCMP with the BNN_3-azidation offers a completely metal-free synthetic route of azido-end polymers. The use of the non-polar solvent further uniquely enabled the azidation of hydrophobic polymers that are insoluble in polar solvents.

Results and Discussion

We first studied the BNN_3-azidation in low molar mass systems. For tertiary alkyl halides, we used ethyl 2-iodo-2-methylpropionate (EMA–I) and ethyl 2-bromo-2-methylpropionate (EMA–Br) (Figure 1), which are unimer models of polymethacrylate–iodide and polymethacrylate–bromide, respectively. A mixture of EMA–I (40 mM) and BNN_3 (60 mM) was heated at 50 °C in a nonpolar solvent, *i.e.*, toluene-d_8. As the ^{1}H NMR spectra show (Figure 2), the azidation was very fast and completed within 20 min (Table 1, Entry 2).

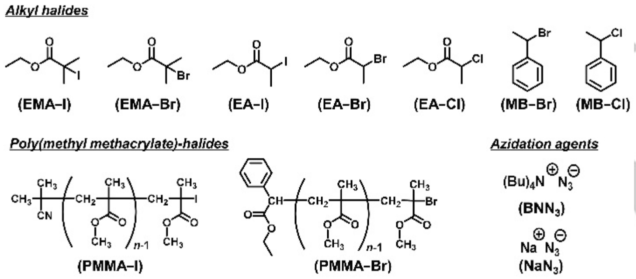

Figure 1. Structures of alkyl halides, poly(methyl methacrylate)-halides, and azidation agents used in this work.

Density functional theory (DFT) calculation suggested that the total energy change from the reactants (EMA–X and tetramethylammonium azide (Me_4NN_3) as a simplified model of BNN_3 for the calculation) to the corresponding products (EMA–N_3 and Me_4NX) is negative (–91.10 kJ/mol for X = I and –91.63 kJ/mol for X = Br), rationalizing the favorable formation of EMA–N_3 from EMA–Br and EMA–I (Figure S2, Supporting information). Despite the large energy change, the reverse reaction may slowly occur. In the present system, tetrabutylammonium iodide (BNI) (generated from BNN_3) precipitated in toluene-d_8. The poor solubility of BNI in toluene prevents the reverse reaction from occurring, driving the azidation reaction (a Finkelstein-type reaction).[24] The poor solubility of BNI is also beneficial for easy removal of BNI in the post-purification of the obtained alkyl azides.

For comparison, NaN_3 was used instead of BNN_3 in toluene. 18-*Crown*-6-ether was added to dissolve NaN_3. EMA–I (1.0 eq, 40 mM), NaN_3 (1.5 eq), and 18-*crown*-6-ether (1.5 eq) were heated at 50 °C in toluene-d_8, resulting in only 3% azido conversion even after 2 h (Table 1, Entry C1). This result is consistent with our previous finding that the reaction of EMA–I with NaN_3 in toluene predominantly generates EMA$^{\bullet}$ radical rather than EMA–N_3.[21] Although the reason for the predominant radical generation by NaN_3 and the predominant azidation by BNN_3 is unclear at the moment, this result means that the observed rapid azidation is unique to BNN_3. No requirement of expensive 18-*crown*-6-ether to dissolve BNN_3 is also beneficial in the practical use.

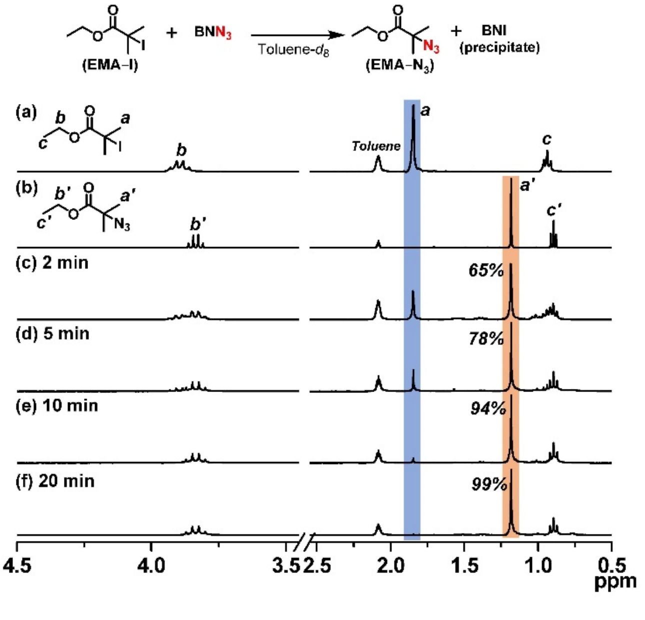

Figure 2. ^{1}H NMR (300 MHz) spectra of (a) pure EMA−I, (b) pure EMA−N_3, and (c−f) a mixture of EMA−I (40 mM) and BNN_3 (60 mM) heated in toluene-d_8 at 50 °C for 2, 5, 10 and 20 min, respectively (Table 1, entry 2).

A reduced amount of BNN_3 from 1.5 eq to 1.2 eq still gave a fast azidation with an almost quantitative (96%) conversion after 45 min at 50 °C (Table 1, Entry 3). Lowering the temperature from 50 °C to room temperature (rt) (20±2 °C) slowed down the reaction but still attained a 96% conversion after 3 h with 1.5 eq of BNN_3 (Table 1, Entry 1).

The azidation of the alkyl bromide EMA–Br was slower than that of the alkyl iodide EMA–I but was still fast. With 1.5 eq of BNN_3, the conversion reached 96% after 1 h at 50 °C and 90% after 6 h at rt (Table 1, Entries 4 and 5), showing the effective azidation of the alkyl bromide.

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Table 1. Azidation of Alkyl Halides and Halide End-functional PMMA.

Entry	R–X (40 mM)	Azide (60 mM)	Solvent	T (°C)	*t* (min)	Conv (%)[a]	*k* (×10^3) (M^{-1} s^{-1})
1	EMA–I	BNN_3	Toluene-d_8	rt	180	96	11
2	EMA–I	BNN_3	Toluene-d_8	50	20	99	190
3	EMA–I	BNN_3[b]	Toluene-d_8	50	45	96	–
4	EMA–Br	BNN_3	Toluene-d_8	rt	360	90	3.2
5	EMA–Br	BNN_3	Toluene-d_8	50	60	96	28
6	EA–I	BNN_3	Toluene-d_8	50	1	99	–
7	EA–Br	BNN_3	Toluene-d_8	50	20	93	–
8	EA–Cl	BNN_3	Toluene-d_8	50	30	98	–
9	MB–Br	BNN_3	Toluene-d_8	50	10	100	–
10	MB–Cl	BNN_3	Toluene-d_8	50	480	85	–
11	PMMA–I	BNN_3	Toluene-d_8	50	10	58	–
					20	96	–
					30	100	–
12	PMMA–Br	BNN_3	Toluene-d_8	50	30	62	–
					60	100	–
C1	EMA–I	NaN_3[c]	Toluene-d_8	50	120	3	0.081
C2	EMA–Br	NaN_3	DMSO-d_6	rt	120	89	6.7
C3	EMA–Br	NaN_3	DMSO-d_6	50	30	99	110

[a] Calculated by ^{1}H NMR spectra. For Entries 11 and 12, the conversions were calculated by using the corresponding PMMA-*b*-PEG copolymers. [b] 48 mM. [c] Addition of 18-*crown*-6-ether (60 mM).

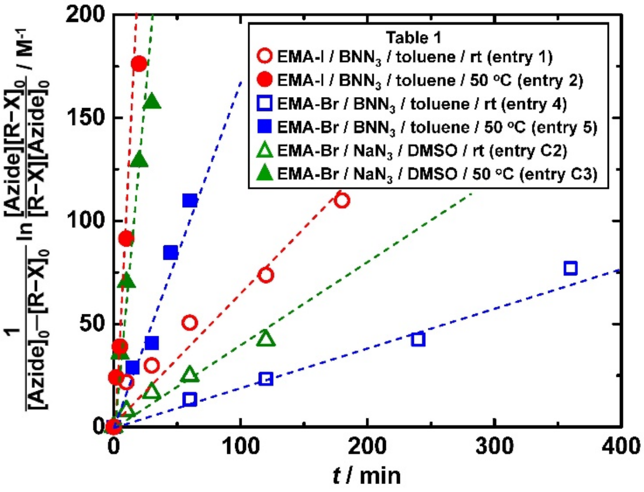

Figure 3. Second-order kinetic plots in the azidation reactions. The alkyl halides, azidation agents, solvents, temperature, symbols are indicated in the figure. The experimental conditions are given in Table 1 (Entries 1, 2, 4, 5, C2, and C3).

The reaction was virtually an irreversible (Finkelstein-type) azidation. We may use the general integrated rate law for the A+B type second-order reaction given by

$$\frac{1}{([\mathrm{BNN_3}]_0-[\mathrm{R{-}X}]_0)}\ln\left(\frac{[\mathrm{BNN_3}][\mathrm{R{-}X}]_0}{[\mathrm{R{-}X}][\mathrm{BNN_3}]_0}\right)=kt \qquad (1)$$

where *k* is the rate constant, R–X is the alkyl halide, and t is the reaction time. Using eq (1), we experimentally deter-mined the k values (Figure 3 and Table 1). The *k* values (M^{-1} s^{-1}) for EMA–I (190×10^{-3} (50 °C) and 11×10^{-3} (rt)) were 3–7 times larger than those for EMA–Br (28×10^{-3} (50 °C) and 3.2×10^{-3} (rt)) (Table 1, Entries 1, 2, 4 and 5). The temperature dependence of this azidation was large, as the k value increased by a factor of 10–20 from rt to 50 °C for EMA–I and EMA–Br. The comparison system with NaN_3/18-*crown*-6-ether has a small *k* value (0.081×10^{-3} (50 °C)) (Table 1, Entry C1).

Using EMA–Br, we also studied the conventional NaN_3-azidation in DMSO. The obtained k values (110×10^{-3} (50 °C) and 6.7×10^{-3} (rt)) (Table 1, Entries C2 and C3) are similar in magnitude to those in the present BNN_3-azidation in toluene (28×10^{-3} (50 °C) and 3.2×10^{-3} (rt)), quantitatively confirming that the BNN_3-azidation in the nonpolar solvent is as effective as the conventional NaN_3-azidation in the polar solvent.

The BNN3-azidation was amenable not only to tertiary alkyl halides but also to secondary alkyl halides, *i.e.*, ethyl 2-iodopropionate (EA–I), ethyl 2-bromopropionate (EA–Br), ethyl 2-chloropropionate (EA–Cl), (1-bromoethyl)benzene (MB–Br), and (1-chloroethyl)benzene (MB−Cl) (Figure 1) at 50 °C using 1.5 eq of NaN_3 (Table 1, entries 6–10). EA–X and MB−X are unimer models of polyacrylate−X and poly-styrene−X, respectively. The reaction of EA−I was extremely fast and completed within 1 min (Table 1, entry 6). Among the alkyl bromides, the reaction was faster in the order of EMA–Br (60 min) < EA–Br (20 min) < MB–Br (10 min for reaching >90% conversion at 50 °C) (Table 1, entries 5, 7, and 9). The BNN_3-azidation was effective even for alkyl chlorides. The reaction of EA–Cl completed in a short time (30 min) (Table 1, entry 8), and that of MB–Cl was relatively slow but still attained a high conversion (85%) after 8 h (Table 1, entry 10).

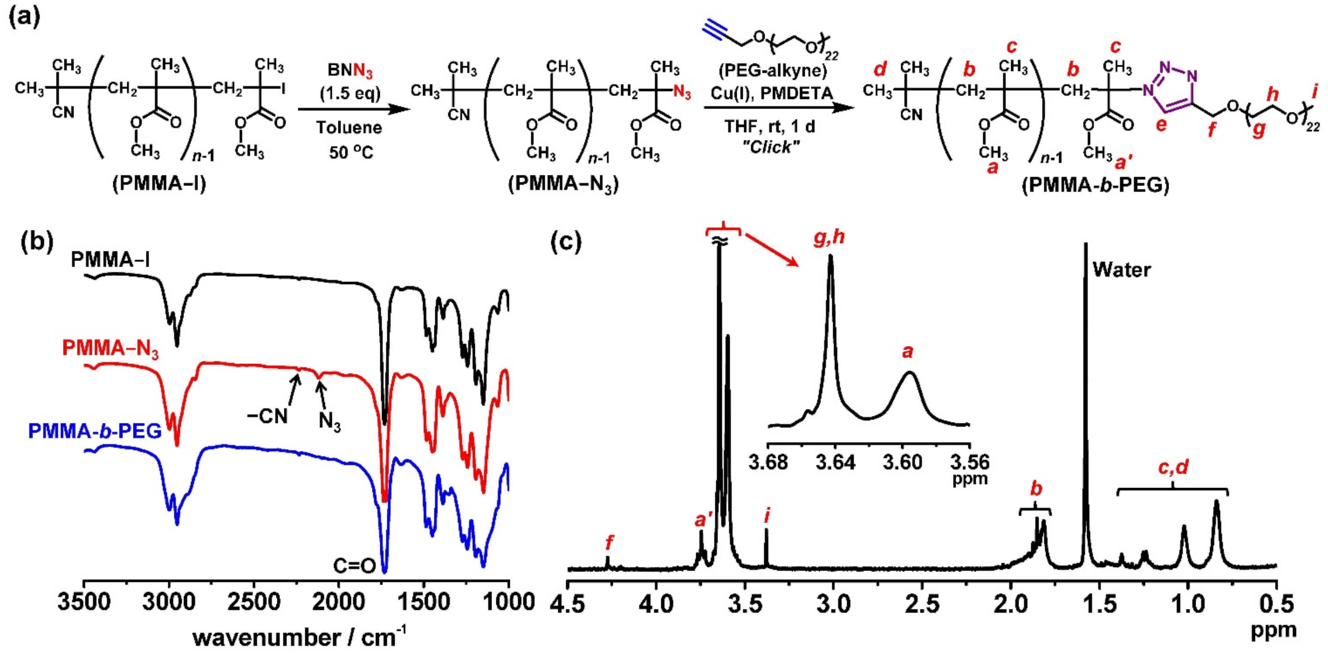

Figure 4. (a) Synthesis of PMMA−N_3 and PMMA-*b*-PEG block copolymer. (b) IR spectra of PMMA−I, PMMA−N_3, and PMMA-*b*-PEG. (c) 1H NMR spectrum ($CDCl_3$) of PMMA-*b*-PEG. The reaction condition is given in Table 1 (Entry 11 for 30 min).

On the basis of the successful azidation of the tertiary alkyl halides (EMA–I and EMA–Br) in the low-mass systems, we studied the chain-end azidation of poly(methyl methacrylate) (PMMA). PMMA–I (M_n = 2600 and $Đ$ = 1.14 after purification) was prepared *via* RCMP of methyl methacrylate (MMA) with 2-iodo-2-methylpropionitrile (CP–I) as an alkyl iodide initiator and tributylmethylphosphonium iodide (BMPI) as an organic catalyst, where $Đ = M_w/M_n$ and M_n and M_w are the number-average and weight-average molecular weights, respectively. PMMA–Br was synthesized via atom transfer radical polymerization (ATRP) of MMA using ethyl *α*-bromophenylacetate (EPh–Br) and a copper(I) catalyst. PMMA–Br was purified by reprecipitation and subsequently by preparative GPC to remove a trace of copper. Recent metal-free photo ATRP may be used to seek a completely metal-free synthesis of PMMA–Br.[25–27]

PMMA–I and PMMA–Br (M_n = 2800 and $Đ$ = 1.11 after purification) were reacted with BNN_3 (1.5 eq) in toluene at 50 °C (Table 1, Entries 11 and 12). The obtained azido-end PMMA (PMMA–N_3) was purified in a robust manner via reprecipitation from a hexane/ethanol (v/v = 4/1) mixture, where the unreacted BNN_3 and the generated BNI were dis-solved in the hexane/ethanol mixture and hence easily re-moved. BNI may also be removed *via* filtration because of its insolubility in the reaction solvent (toluene). The presence of the azide in PMMA–N_3 was confirmed from a peak at 2120 cm^{-1} in the IR spectrum (Figure 4b). For a quantitative analysis of the azide, the obtained PMMA–N3 was reacted with an alkyne-bearing polyethylene glycol (PEG-alkyne, M_n = 1000, $Đ$ = 1.06) *via* CuAAC to give a PMMA-*b*-PEG block copolymer (Figure 4a). After CuAAC, the IR peak of the azide completely disappeared, suggesting a quantitative CuAAC (Figure 4b). Assuming the quantitative CuAAC, from the ^{1}H NMR peak areas for the PMMA (*a*, 3.60 ppm) and PEG (*g* and *h*, 3.64 ppm) segments in PMMA-*b*-PEG (Figure 4c), we estimated the amount of the azide in PMMA–N_3, hence the conversion of PMMA–X to PMMA–N_3. The conversion was virtually 100% in 30 min for PMMA–I and in 60 min for PMMA–Br at 50 °C (Table 1, Entries 11 and 12). This result demonstrates that the BNN_3-azidation is highly effective in polymer systems, enabling rapid and quantitative synthesis of azido-end PMMA from both iodo- and bromo-end PMMAs.

The BNN_3-azidation also enabled the synthesis of various azido-end polymethacrylates, including diazido-end PMMA (N_3–PMMA–N_3), triazido-end PMMA (3-arm star PMMA–N_3), azido-end poly(lauryl methacrylate) (PLMA–N_3), azido-end poly(2-methoxyethyl methacrylate) (PMEMA–N_3), azido-end poly(2,2,2-trifluoroethyl methacrylate) (PTFEMA–N_3), and azido-end poly(methyl methacrylate)-*b*-poly(benzyl methacrylate) (PMMA-*b*-PBzMA–N_3) (Table S1 and Figures S24–S29, Supporting information). Particularly, hydrophobic PLMA–N_3 is insoluble in polar solvents and hence is unable to synthesize in the conventional NaN_3-azidation using polar solvents. Therefore, the synthesis of PLMA–N_3 is unique to the present BNN_3-azidation using the nonpolar solvent. The fast reaction and broad polymer scope are highly beneficial for practical applications.

Conclusions

In conclusion, a novel and effective azidation method using BNN_3 in a nonpolar solvent was successfully developed. This method enabled the synthesis of functional azido-end polymethacrylates without using a large excess of BNN$_3$ in a short reaction time (≤ 60 min). The rapid and quantitative reaction, no use of any metals or polar solvents, and broad scope in alkyl halides and polymethacrylates are attractive and unique features of this azidation.[28]

Experimental Section

Synthesis of PMMA−I.

A mixture of MMA (10.0 g, 100 mmol), CP−I (0.66 g, 3.37 mmol), BMPI (0.60 g, 1.75 mmol), and toluene (3.33 g) was heated in a 50 mL flask at 60 °C under argon atmosphere with magnetic stirring. After 4 h, the mixture was quenched to room temperature and diluted with THF (15 mL). The polymer was reprecipitated in hexane (300 mL), collected by filtration, and dried in vacuo to give PMMA−I (6.62 g); monomer conversion = 72%; M_n = 2600 and $Đ$ = 1.14 after purification.

Synthesis of PMMA−Br.

A solution of MMA (5.0 g, 50 mmol), EPh−Br (0.82 g, 3.37 mmol), and CuBr (71.6 mg, 0.50 mmol) in a Schlenk flask was purged with argon for 5 min. In the second Schlenk flask, a solution of MMA (5.0 g, 50 mmol) and *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine (PMDETA, 0.17 g, 1.00 mmol) was purged with argon for 5 min. The solution in the second flask was transferred to the first flask under argon atmosphere through a degassed syringe. The reaction mixture was heated at 80 °C under argon atmosphere with magnetic stirring. After stirring for 3 h, the reaction mixture was diluted with THF (10 mL), filtrated, and reprecipitated in hexane (300 mL). The obtained solid was further purified by preparative gel permeation chromatography to give PMMA−Br (6.40 g); monomer conversion = 69%; M_n = 2800 and $Đ$ = 1.11 after purification.

Synthesis of PMMA−N$_3$.

In a typical run, PMMA−I (M_n = 2600, $Đ$ = 1.14, 40 mM) or PMMA−Br (Mn = 2500, Đ = 1.12, 40 mM) and BNN$_3$ (60 mM) were dissolved in toluene. The reaction mixture was heated at 50 °C with stirring. After a prescribed time *t*, the reaction solution was reprecipitated in hexane/ethanol (v/v = 4/1, 100 mL) mixture. The polymer was collected and dried in vacuo to give PMMA−N$_3$. The other functional azido-end polymethacrylates were prepared similarly with BNN$_3$ in toluene.

Copper-catalyzed azide-alkyne cycloaddition of PMMA−N$_3$ with alkynes.

In a typical run, a solution of PMMA−N$_3$ (M_n = 2800, $Đ$ = 1.13, 150 mg, 0.058 mmol) and CuBr (12.4 mg, 0.087 mmol) in THF (1.0 mL) in a Schlenk flask was purged with argon. In the second Schlenk flask, a solution of PMDETA (30.1 mg, 173 mmol) and PEG-alkyne (90.0 mg, 0.087 mmol) in THF (1.0 mL) was purged with argon for 2 min. (The syntheses of PEG-alkyne are described in a previous publication.[19]) The solution in the second flask was transferred to the first flask under argon atmosphere through a degassed syringe. After stirring for 24 h at room temperature under argon atmosphere, the solution was filtered to remove the precipitated salts. The remaining polymer solution was purified by reprecipitation in methanol/water (v/v = 2/1) or using preparative GPC to remove unreacted PEG-alkyne. The PMMA-*b*-PEG block copolymer was dried in vacuo.

Acknowledgements

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Conflict of interest

The authors declare no competing financial interest.

Keywords: azidation • tetrabutylammonium azide • polymethacrylate • click reaction • metal-free

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Layout 1:

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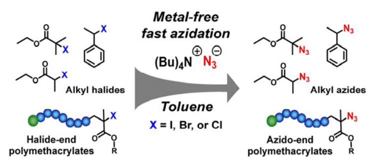
An effective method to synthesize azido-end polymethacrylates using tetrabutylammonium azide (BNN$_3$) was developed. Alkyl halides and polymethacrylate-halides were reacted with BNN$_3$ in toluene to generate the corresponding azides. The azidation was rapid and quantitative without using a large excess of BNN$_3$, any metals, or polar solvents.



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Metal-Free Fast Azidation Using Tetrabutylammonium Azide: Effective Synthesis of Alkyl Azides and Well-defined Azido-end Polymethacrylates