SuFEx + ATRP

- 😊 Quantitative
- 😊 Fast Reaction
- 😊 Robust

Combination of AGET ATRP and SuFEx for Post-Polymerization Chain-end Modifications

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Highlights: Sulfur(VI) Fluoride Exchange, AGET ATRP, Chain-end Modification

Abstract

Post-polymerization modification of polymer chain-ends is a powerful tool for the preparation of functional materials. “Click” type reactions represent the most prevalent post-polymerization strategies. We applied the recently described sulfur(VI) fluoride exchange reaction to functionalize the chain-ends of four polymers prepared using activators generated by electron transfer atom transfer radical polymerization. Aryl-TBDMS terminated polymers were reacted with aryl sulfurofluoridate compounds with a near quantitative conversion. This research represents the application of a new click type reaction to prepare functional polymers.

Introduction

Post-polymerization modification is a critical tool to prepare tailor made materials for a range of applications including functional polymers,¹⁻⁴ electronic/optoelectronic materials,⁵⁻⁸ bioconjugates,⁹⁻¹⁴ drug delivery,¹⁵⁻¹⁷ and biomaterials.¹⁸⁻²⁰ There are several critical factors that determine the utility of a chemical reaction’s use to modify polymers. These factors include yields, ease of reagent synthesis and purification, air and moisture sensitivity, and reaction times. “Click” type reactions including Cu(I) catalyzed azide alkyne cycloaddition,^{3, 21-24} thiol-ene coupling,²⁵⁻²⁷ oxime ligation,²⁸⁻³⁰ diels-alder,^{31, 32} and thio-bromo exchange³³⁻³⁵ uniquely fit the required factors and have found wide spread adoption for chain-end post-polymerization modification. Nevertheless, it is always challenging yet necessary to utilize new types of “click” reaction in post-polymerization modification with easier setup, cleaner reaction, and wider application range.

A new “click” type reaction was recently reported by Sharpless and coworkers³⁶ named the sulfur(VI) fluoride exchange (SuFEx) reaction, which utilizes sulfur(VI) fluorides and has drawn great attention for its easy synthesis, high-tolerability to various reaction conditions and functional groups, fast reactions and high yields. Compounds containing S^{VI}-F groups, including sulfonyl fluoride (–SO₂F), fluorosulfate (–OSO₂F), and sulfamoyl fluoride (–NSO₂F), can be readily prepared by conversion from sulfonyl chloride (–SO₂Cl)³⁷ or by reactions of alcohols and amines with SO₂F₂ gas under basic conditions.³⁶ The S^{VI}-F groups are relatively stable and inactive under a number of reaction conditions. Moreover, the S^{VI}-F group can be specifically reacted with certain functional groups (e.g. silane, secondary amine) to eliminate the fluorine while forming a stable sulfuryl linkage (–SO₂–) between the two components,^{36, 38, 39} which demonstrates the potential of using these reactions in linking chemistry. These SuFEx reactions have been demonstrated to be orthogonal, metal-catalyst-free, efficient (i.e. high conversion) and simple to setup with no sensitivity to moisture or oxygen. In this communication, we utilized the reaction between arylsulfonyl fluorides and aryl silyl ethers to prepare stable arylsulfate modified chain-ends for polymers. As proof of concept, we report for the first time the successful chain-end modification of polymers with tert-butyltrimethylsilyl ether (TBDMS) end group by reaction with small molecule arylsulfonyl fluorides.

Scheme 1 Synthesis of TBDMS end-functionalized polymers, the model sulfurofluoridate compounds, and the subsequent sulfur fluoride exchange reactions. Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2 , rt; (b) CuBr_2 , TPMA, ascorbic acid, DMF, 40 °C; (c) CuBr_2 , TPMA, ascorbic acid, DMF, 60 °C; (d) Et_3N , CH_2Cl_2 , rt; (e) Et_3N , CH_2Cl_2 , rt, then DBU, DMF, 80 °C; (f) DBU, DMF, 80 °C.

Results and discussion

Initiator Synthesis

ATRP initiators were prepared with terminal TBDMS ethers to introduce the reactive handle required for the SuFEx reaction. Two different TBDMS ether functional ATRP Initiators were prepared (Scheme 1) from 2-[4-(tert-butyldimethylsilyloxy)phenyl]ethanol (**TBDMS-OH**), which was synthesized by the reaction of TBDMS-Cl with 2-(4-hydroxyphenyl)ethanol. This intermediate was used to prepare the two initiators, **TBDMS-iBBr** and **TBDMS-BPA**, via EDC/DMAP catalyzed esterification (see Scheme 1). The structure and purity of the initiators was confirmed by ^1H NMR.

To demonstrate the applicability of the SuFEx reaction to a wide range of polymer substrates, including hydrophilic and hydrophobic (meth)acrylates, the following polymers were prepared using AGET ATRP.^{40, 41} TBDMS-poly(methyl methacrylate) (**TBDMS-PMMA**), TBDMS-poly(butyl acrylate) (**TBDMS-PBA**), TBDMS-poly(oligo(ethylene oxide) methacrylate) (**TBDMS-POEOMA**), and TBDMS-poly poly(oligo(ethylene oxide) acrylate) (**TBDMS-POEOA**). The polymerization kinetics were monitored using ^1H NMR and evolution of molecular weight was followed using GPC analysis.

Polymer Synthesis and Characterization

The polymers had linear reaction kinetics with good control over molecular weight and molecular weight distribution in the final polymers. The TBDMS-PMMA molecular weight was higher than theory potentially due to initiator termination. The POEOMA and POEOA samples had an apparent molecular weight lower than theoretically predicted potentially due to the use of linear poly(ethylene glycol) standards on the aqueous GPC ($M_{n, \text{TBDMS-PBA}} = 3040$, $M_w/M_n = 1.10$; $M_{n, \text{TBDMS-PMMA}} = 4020$, $M_w/M_n = 1.09$; $M_{n, \text{TBDMS-POEOMA}} = 9370$, $M_w/M_n = 1.38$; $M_{n, \text{TBDMS-POEOA}} = 2890$, $M_w/M_n = 1.12$) (see Table 1). Low conversions were targeted to ensure retention of active chain-ends and to aid ^1H NMR characterization. The polymers were isolated by dialysis and the structures of them were confirmed by ^1H NMR (see Supporting Information).

Table 1 AGET ATRP using TBDMS initiator

I		time/min	conv./%	$M_{n, \text{theo}} \times 10^{-3}$	$M_{n, \text{GPC}} \times 10^{-3}$	M_w/M_n
TBDMS-PMMA	TBDMS-BPA	70	21	2.5	4.0	1.09
TBDMS-PBA	TBDMS-iBBr	350	17	2.6	3.0	1.10
TBDMS-POEOMA	TBDMS-BPA	70	44	22.4	9.4	1.38
TBDMS-POEOA	TBDMS-iBBr	120	23	11.4	2.9	1.12

SuFEx Chain-end Modification

The SuFEx reaction was carried out between the TBDMS end-functionalized polymers and two model compounds, phenyl sulfurofluoridate (**Ph-OSO₂F**) and vinylphenyl sulfurofluoridate (**St-OSO₂F**). These model compounds were selected for their structures simplicity in NMR characterization and/or potential usage in macromonomer synthesis. The model compound **Ph-OSO₂F** was synthesized by reactions of phenol with the SO_2F_2 gas according to a published procedure.³⁶ **St-**

OSO₂F was prepared from 4-(2-bromoethyl)phenol by a one-pot reaction to add -SO₂F group at the phenol end and elimination of the ethyl bromide to vinyl group with DBU as a base. ¹H NMR spectra confirmed the formation of **Ph-OSO₂F** and **St-OSO₂F**. As shown in Fig. 1, **Ph-OSO₂F** showed multiple proton signals between 7.3 ~ 7.7 ppm in the aromatic region, which are reasonably higher than the chemical shift of aromatic protons of phenol as a result of the -SO₂F group attachment. For the **St-OSO₂F**, NMR signals from aromatic protons (7.6~7.3 ppm) and protons from the vinyl group (6.74, 5.80, 5.38 ppm) can all be observed and assigned (see Fig. 2). The incorporation of the -SO₂F group on both the products was also confirmed by ¹⁹F NMR (see Fig. S5 & S6 in Supporting Information).

Fig. 2 ¹H NMR spectra of **St-OSO₂F**, **TBDMS-PBA** and **St-SO₂-PBA**. X (symbol) denotes solvent peaks.

The two model compounds were reacted with both **TBDMS-PMMA** and **TBDMS-PBA** with DBU as a catalyst. The aryl sulfonylfluorides were used in a 10 times equivalent excess of polymers to ensure a complete end-group conversion (see Supporting Information for the reaction conditions). Polymers before and after the reaction were analyzed by ¹H NMR spectroscopy. Fig. 1 showed the ¹H NMR spectra of **Ph-OSO₂F**, **TBDMS-PMMA** and **Ph-SO₂-PMMA**. In the NMR of **TBDMS-PMMA**, the proton peaks from the TBDMS chain-end group can be clearly identified. The two NMR signals marked as a' and b' are attributed to the aromatic protons from the OTBDMS-phenyl group, and the peaks marked as a, b and c are attributed to the aryl protons from the phenyl acetate. Proton signals from TBDMS groups can also be observed and marked as 2 and 3. The spectrum of the product confirmed successful reaction: signals at a' and b' were shifted to higher position due to the replacement of -TBDMS group with -SO₂Ph. The cleavage of the end -TBDMS groups was also evidenced by the disappearance of peaks at 2 and 3. The ratio of the integrations of all polymer aromatic peaks before and

Fig. 1 ¹H NMR spectra of **Ph-OSO₂F**, **TBDMS-PMMA** and **Ph-SO₂-PMMA**. X (symbol) denotes solvent peaks.

after the SuFEx reaction was calculated to be $0.26/0.18 = 1.45$. Comparing to the theoretical ratio if all the end groups are reacted (theoretically $14/9 = 1.56$), these results indicated that the SuFEx chain-end modification reaction had a near quantitative conversion.

The SuFEx reaction was applied to the synthesis of macromonomers via incorporation of the newly reported **St-OSO₂F** monomer. Similar reaction conditions were applied, and the ¹H NMR spectra of the products indicated reaction completeness (see Fig. 2 for **TBDMS-PBA** and Fig. S1 for **TBDMS-PMMA** in Supporting Information). As shown in Fig. 2, the conversion of the end-groups of PBA was quantitative: the proton signals from the –TBDMS group (marked as 2 & 3 in Fig. 2) disappeared in the spectrum of the product. Additionally, the proton peaks of the phenyl end-group (marked as a & b in Fig. 2) moved to a higher chemical shift (~7.7 ppm), similar to what was observed in the reaction of **TBDMS-PMMA** and **Ph-OSO₂F**. After the reaction, the proton peaks from the vinyl group can be clearly identified and were assigned as 2, 3 and 4, respectively. The integration of the aromatic protons in the product was twice as much as that of the starting polymer ($0.32/0.16 = 2$), which perfectly matches the theoretical aromatic proton ratio before and after reaction ($8/4 = 2$). These results clearly demonstrate the complete conversion of the end-group of the polymers to –OSO₂–styrene. Such styrene-ended polymers can be utilized as macromonomers and preparation of SuFEx enabled functional polymers with complex architectures (e.g. block copolymers, hyperbranched polymers, brush polymers) will be the subject of future studies.

Fig. 3 (a) ¹H NMR spectra of **Qn-SO₂F**, **TBDMS-POEOA** and **Qn-POEOA**. (b) GPC traces of **TBDMS-POEOA** before and after the SuFEx reaction with **Qn-OSO₂F**.

Dye labeled polymers have found utility in a range of biological applications including monitoring of polymer internalization and cell labelling. Therefore we introduced a arylsulfonyl fluoride derivative of 8-hydroxyquinoline (see Scheme 1). 8-hydroxyquinoline and its derivatives have been utilized as chelating agents and photonic materials in biological applications.^{42, 43} Furthermore use of this dye facilitates conclusive determination of chain-end incorporation using GPC with a UV-vis detector. 8-hydroxyquinoline has UV absorption between 200 and 360 nm with a peak at ~310 nm, and was thus selected as a model of biorelevant small molecule dye in incorporation at the polymer chain-end for the quantification of the reaction using GPC with UV-absorbance. 8-hydroxyquinoline was first converted to 8-(OSO₂F)-quinoline (**Qn-OSO₂F**) by reaction with SO₂F₂ gas and the structure of the product was confirmed by ¹H and ¹⁹F NMR (see Figure S7 & S8 in Supporting Information). The absorption of the modified dye also shifted to lower wavelength with an absorption peak at 280 nm and absorption edge at ~350 nm (see Figure S9 in Supporting Information). **Qn-OSO₂F** was then reacted with two

water soluble polymers, **TBDMS-POEOMA** and **TBDMS-POEOA**. GPC studies confirmed the incorporation of the dye to the polymers. Figure 3 shows the proton NMR spectra and the GPC traces of TBDMS-POEOA before and after reaction. As shown in Figure 3a, the shift of the phenyl proton peaks (marked as a & b) and the appearance of the quinoline proton peaks confirmed the conversion of the polymer end group. In the GPC traces in Figure 3b, the RI signals of Qn-POEOA shifted to higher molecular weight position comparing that of TBDMS-POEOA, and a similar molecular weight increase was also observed for Qn-POEOMA (see Figure S11 in Supporting Information). For UV signals in GPC, both POEOMA-dye and POEOA-dye showed enhancement in absorption at 280 nm in GPC (see Figure S12 in Supporting Information). In addition, both of the dye-modified polymers showed clear UV signals at absorption of 309 nm (Figure 3b and Figure S11 in supporting information), of which wavelength the original polymer have minimal absorption and thus the newly appeared absorption should be attributed to the incorporation of the dye. All these facts indicate the successful conversion of TBDMS group at the polymer chain-end to the dye molecule. The incorporation of a dye molecule using SuFEx should allow for the tracking of modified biocompatible polymers in cell culture and will be the subject of future research.

Conclusion

In conclusion, we reported for the first time the end-functionalization of polymers using the simple and efficient SuFEx click chemistry reaction. Four polymers with a SuFEx reactive handle (i.e. aryl TBDMS) were prepared using AGET ATRP including PMMA, PBA, POEOMA, and POEOA. To demonstrate the efficacy of the SuFEx reaction **TBDMS-PBA** and **TBDMS-PMMA** were ligated with two small molecules bearing the suitable reactive partner (**Ph-OSO₂F** and **St-OSO₂F**). ¹H NMR studies of the products reveals that the reactions proceeded well with a near 100% conversion. To further demonstrate the utility of the SuFEx reaction as a useful tool in polymer chain end modification a dye (**Qn-OSO₂F**) was conjugated to **TBDMS-POEOMA** and **TBDMS-POEOA**. ¹H NMR and GPC with dual RI and UV detection were then utilized to confirm incorporation of Qn to the polymer chain-end. Comparing to other click reactions, the functional groups used in SuFEx reaction are relatively more stable to temperature and do not require the use of potentially toxic transition metal. **A major study is underway expanding the scope of the SuFEx reactions in post-polymerization functionalization.**

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