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SYNTHESIS OF THE NEW MONOMER 3-(N-PYRIMIDIN-2-YL-N(-4-ACETYLAMINO-BENZENESULFONYL)AMINO-1-PROPENE, ITS COPOLYMERIZATION WITH MALEIMIDE AND HYDROLYSIS OF COPOLYMER

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SYNTHESIS OF THE NEW MONOMER 3-(N-PYRIMIDIN-2-YL-N(-4-ACETYLAMINO-BENZENESULFONYL)AMINO-1-PROPENE, ITS COPOLYMERIZATION WITH MALEIMIDE AND HYDROLYSIS OF COPOLYMER

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Key Words: 3-(N-pyrimidin-2-yl-N(-4-acetylaminobenzenesulfonyl)amino-1-propene, Maleimide, Copolymerization

ABSTRACT

A new monomer, 3-(N-pyrimidin-2-yl-N(-4-acetylaminobenzenesulfonyl)amino-1-propene(PABP) (M_1), was prepared using sulfadiazine as parent compound, and characterized by IR and ^{1}H-NMR in detail. It was reluctant to homopolymerize, but could be copolymerized with maleimide (MI) (M_2) in dimethylformamide at 60°C using AIBN as an initiator. The copolymerization rate and monomer conversion decreased with an increase of PABP contents in feed ratio because of the chain transfer of propagation species to PABP. After hydrolysis with 15% HCl, the copolymer bearing sulfadiazine as a pendant was obtained.

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INTRODUCTION

It is well known that sulfadiazine and its homologs are widely used for the prevention and therapy of bacterial infection in local and the whole body [1-3]. In 1950, however, Steven *et al.* Found [4] that sulfadiazine could be concentrated selectively in the Walker carcinoma growing in rats with the ratio of 4:1 for tumor cell vs normal cell. Since then much work was focused on the modification of sulfadiazine in order to combine its selective concentration in malignant tissue with some anti-tumor drugs [5, 6].

In the sulfadiazine, there are two reactive sites, one is aromatic amine, the other is sulfonamide. At present, overwhelming work of modified sulfadiazine was centered on the former case [7-9], only a few reports [10-12] were connected with the latter because of its lower activity, space hindrance and poor solubility in common solvents.

On the other hand, maleimide and its derivatives could be used to improve the thermal stability and adhesiveness of polymer materials by copolymerization with other monomers [13]. Fields *et al.* [14] found that a low molecular weight copolymer with 14-25% of succinimide rings in the main chain is effective against several transplantable tumors. Cho *et al.* [15, 16] confirmed that the poly (N-glycinylmaleimide-co-methacrylic acid) and poly (N-glycinylmaleimide-co-vinyl acetate) showed the antitumor activity *in vivo*. These investigations have opened up a new frontier for the pharmaceutical applications of maleimide.

In order to combine the merits of sulfadiazine and maleimide together, a new monomer 3-(N-pyrimidin-2-yl-N(-4-acetylaminobenzenesulfonyl)amino-1-propene was prepared successfully by us, and the present paper is only focused on the copolymerization of this monomer with maleimide.

EXPERIMENTAL

Materials

Sulfadiazine (Shanghai Sanwei Pharmaceutical Ltd. Co, China) was purified by a solvent mixture of dimethyl sulfoxide (DMSO) and alcohol (v/v: 9/1). Allyl Bromide (Shanghai First Reagent Factory, China) was dried with $CaCl_2$, and then distilled before use. Acetyl chloride was prepared by the reaction of acetic acid with phosphorus chloride. Maleic anhydride (Shanghai Third Reagent Factory) and urea (Wuxi Mingfeng Reagent Factory) were used as

received. AIBN was recrystallized twice from methanol. All other reagents were purified by standard methods.

Preparation of p-Acetylamino-N-(pyrimidin-2-yl) Benzene Sulfonamide (II)

In a three-necked 250 mL flask equipped with a condenser, dropping funnel, and mechanical stirrer, 25 g (0.1 mol) of sulfadiazine dissolved in 200 mL pyridine was placed, and the flask was cooled to 1-4°C in an ice bath, and then 10 mL (0.14 mol) of acetyl chloride was added dropwise in 30 minutes with stirring. The reaction was continued for about 3 hours under stirring at room temperature, then the solution was concentrated to half of its original volume and poured into distilled water. The product was purified by recrystallization with dioxane in the yield of 88%. IR (KBr, cm^{-1}): 3311 (ν_{N-H} of $-NHCOCH_3$), 3274 (ν_{N-H} of $-SO_2NH-$), 1678 ($\nu_{C=O}$), 1597, 1490, 1446 ($\nu_{phenyl\ ring}$); ^{1}H-NMR (DMSO-d_6, ppm): 2.1 (s, 3H, $-CH_3$), 10.3 (s, 1H, -CONH-), 11.7 (s, 1H, - SO_2NH-), 7.0-8.5 (pyrimidinyl ring), 7.7-7.9 (phenyl); m.p. 263-264°C.

Preparation of p-Acetylamino-N-(pyrimidin-2-yl) Benzene Sulfonamide Sodium Salt (III)

To an aqueous solution of sodium hydroxide (0.2 g in 200 ml), 14.6 g (0.05 mol) of p-acetylamino-N-(pyrimidin-2-yl) benzene sulfonamide (II) was added, and the solution was stirred and gently warmed until all of (II) was dissolved and *p*H of the solution dropped to about 8. After filtration, the filtrate was condensed under reduced pressure until no water could be distilled. The product (III) was purified by recrystallization with ethyl alcohol (yield, 75%). IR (KBr, cm^{-1}): 3355 (ν_{N-H} of $-NHCOCH_3$), 1662 ($\nu_{C=O}$), 1590, 1448 ($\nu_{phenyl\ ring}$); ^{1}H-NMR (DMSO-d_6, ppm): 2.0 (s, 3H, $-CH_3$), 10.0 (s, 1H, -CONH-), 6.3, 8.0 (pyrimidinyl ring), 7.5-7.7 (phenyl).

Preparation of 3-(N-Pyrimidin-2-yl-N'-4-acetylaminobenzenesulfonyl)-amino-1-propene (IV)

The sulfonamide sodium salt (III) (14.5 g, 0.046 mol) and N, N-dimethyl formamide (250 mL) were charged in a 500 mL round-bottomed flask equipped with a condenser. The mixture was heated to 80°C with stirring and maintained at this temperature for 10 minutes, and then allyl bromide (14 g, 0.12 mol) was added and reaction was proceeded for about 12 hours under gentle reflux. The solution was concentrated to 1/3 of its original volume under reduced pressure and then poured to an aqueous solution of sodium hydroxide (*p*H 8). The crude

product was recrystallized twice from distilled water, yield was 44%, and m.p.: 210-211°C.

Preparation of Maleimide

Maleimide was prepared according to the literature [17]. The m.p of the product recrystallized from ethyl acetate was 93-94°C. It was further purified by sublimation under vacuum before use with the yield 48%. IR (KBr, cm^{-1}): 1772, 1698 ($\nu_{C=O}$), 1577 ($\nu_{C=C}$), 3196 (ν_{NH}); ^{1}H NMR (δ:: ppm): 10..9 (s, 1H, -NH-), 6.9 (s, 2H, -CH=CH-).

Copolymerization

Accurately weighed PABP (M_1), MI (M_2), AIBN and a given amount of DMF were placed into a 100 mL glass ampoule and degassed three times by freeze-pump-thaw at 77 K, then sealed off under N_2. The copolymerization of different monomer feed ratios was performed in DMF at 60 ± 0.1°C. After a given time, the ampoules were removed from the oil bath and the contents were poured into a large excess of diethyl ether. The precipitate was further extracted with acetone in Soxhlet for 24 hours to remove the unreacted PABP and MI.

Homopolymerization of PABP and MI

MI was polymerized using the similar procedure described before and the product was further purified with diethyl ether in Soxhlet extractor for 24 hours. The polymer of white powder was obtained. IR (KBr, cm^{-1}): 1782, 1701 ($\nu_{C=O}$), 3548, 3269 ($\nu_{C=O}$); ^{1}H-NMR (DMSO-d_6, ppm): 10.8-12.4 (-CONHCO-), 3.0-4.4 (-CH-CH-).

The monomer PABP was difficult to homopolymerize, the polymerization procedure was conducted as follows: a solution of 2.6 g of PABP monomer, 8mL of DMF, and 0.02 g of AIBN was placed into a 100-mL glass ampoule and degassed three times by freeze-pump-thaw at 77 K, then sealed off under N_2. Polymerization was conducted at 60 ± 0.1°C for 68 hours, and then the solution was poured slowly into acetone. No polymer was found, and after evaporation of the solvent, all the PABP was left.

Hydrolysis of Copolymer

To a solution of the copolymer (0.1 g) in 30 mL of a mixed solvent of acetone and water (v/v 2:1) 5 mL of 15% HCl was added, and the system was refluxed for 3 hours. After the solution was cooled to room temperature, sodium

carbonate was slowly added until no bubble appeared. The solution was kept at room temperature overnight. After filtration, the hydrolized solid was isolated by evaporating acetone under reduced pressure. The product was washed three times with water, and then dried in vacuum oven, yielding 0.09 g.

Instruments

^{1}H-NMR spectra were recorded on a Bruker MSL-300 spectrometer with tetramethylsilane (TMS) as the internal standard and DMSO-d_6 as a solvent. IR spectra were obtained on a Magna-550 FTIR spectrometer.

Measurements of Viscosity and Copolymerization Rate (R_p)

Intrinsic viscosity [η] of the copolymers was calculated by the following relationship [18]:

$$[\eta] = [\eta]_{sp} / [c\,(1+0.333\eta_{sp})]$$

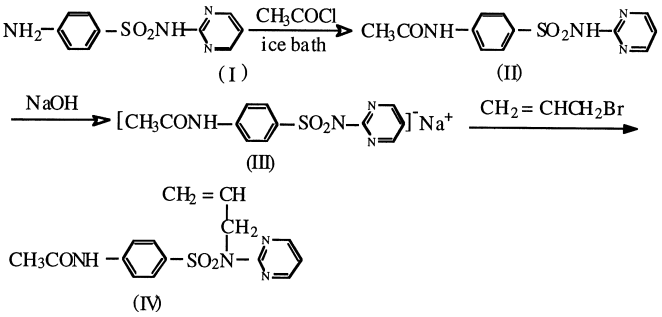
(η_{sp} = specific viscosity, c = conc. in g/cm^3)

The viscosity of the copolymers (copolymer concentration less than 0.1g/cm^3) was obtained with an Ubbelohde viscometer at 30 ± 0.1°C. The copolymerization rate (R_p) was evaluated by the gravimetric method.

RESULTS AND DISCUSSION

Monomer Characterization

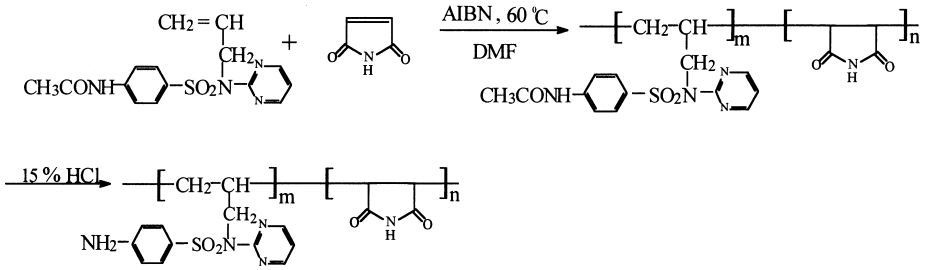
The monomer, 3-(N-pyrimidin-2-yl-N(-4-acetylaminobenzenesulfonyl)amino-1-propene (PABP), was prepared according to Scheme 1. PABP forms yellowish crystalline needles with a m.p. of 210-211°C. It is easily dissolved in N, N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), hot acetone, and hot acetonitrile. The structure of PABP was confirmed by ^{1}H-NMR as shown in Figure 1(a), in which all the proton chemical shifts at 10.3 (s, 1H, -CONH-), 7.7, 7.9 (phenyl ring), 7.1, 8.5 (pyrimidinyl ring), 5.9 (m, 1H, -CH = CH_2), 5.1 (m, = CH_2, -CH = CH_2), 4.7 (d, 2H, -CH_2-CH = CH_2) and 2.0 (s, 3H, -CH_3) ppm agree with the structure. The same conclusion could also be derived from its IR spectrum with the absorption at 3392 cm^{-1} attributed to ν_{N-H} of -NHCOCH$_3$, at 1702 cm^{-1} to carbonyl group, at 1647 cm^{-1} to double bond and 1593, 1436 cm^{-1} to phenyl ring.



Scheme 1.

Copolymerization of PABP with MI

The copolymerization of PABP with MI can be represented as the following equations (Scheme 2):



Scheme 2.

The copolymers were obtained as a yellowish powder, easily soluble in DMF, DMSO and a mixed solvent of acetone and water. Figure 1 (b) shows a ^{1}H-NMR spectrum of copolymer. In the copolymer, the signals at 5.1-5.9 ppm, corresponding to protons of the -CH = CH_2 group of PABP, disappeared. In addition, we also observed proton resonance due to MI at 11.5 ppm, indicating that PABP was copolymerized with MI.

Effect of Feed Ratio on Copolymerization

In order to determine the copolymer compositions, the ratio of imide proton and phenyl proton signals in the NMR spectrum was measured. MI molar fraction in the copolymers was obtained using the following equation:

$$\mathrm{MI(mol\%)} = \frac{A_1 \times 4}{A_1 \times 4 + A_2}$$

where MI (mol%) is the mol fraction of maleimide in the copolymers, A_1 is the integrated area of the imide (-NH-) proton in maleimide unit and A_2 is the integrated area of the phenyl(-C_6H_4-) proton in the PABP unit.

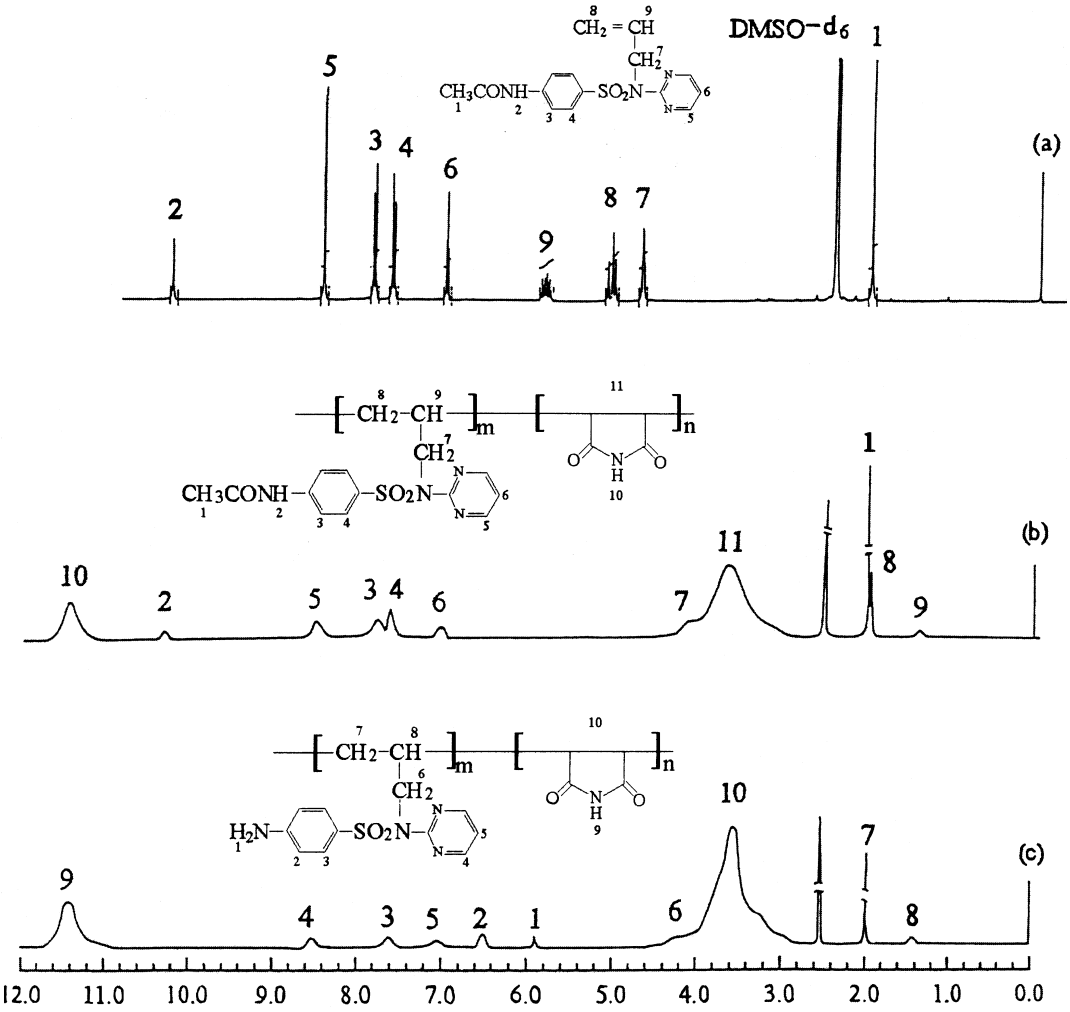


Figure 1. ^{1}H-NMR spectra of PABP (a), its copolymers (b) (MI in feed: 81.6 mol%) and copolymer after hydrolysis (c).

TABLE 1. Effect of Monomer Feed on Copolymerization[a]

Monomer Feed		R_p	Conversion	Copolymer Composition	$[\eta]^c$
MI (g)	MI (mol%)	(%/h)	(%)	MI (mol%)	(cm^3/g)
0.778	100	2.38	33.3	100	10.17
0.699	90.0	1.49	9.3	94.8	9.72
0.633	81.6	0.17	3.1	90.8	7.57
0.582	75.5	–	6.3	87.2	–
0.544	70.0	0.03	1.2	84.5	8.03
0.466	60.1	0.01	<1.0[b]	–	–
0.388	49.9	–	**	–	–
0.311	40.0	–	**	–	–

[a] AIBN: 0.12mmol; $[M_1] + [M_2]$ = 8 mmol; solvent, DMF (8 mL), temperature: 60°C

[b] Reaction time: 73 hours

[c] Solvent, DMF; temperature, 30 ± 0.1°C

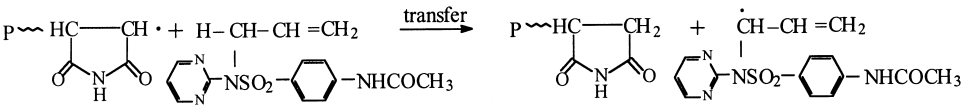
**Only a negligible amount of copolymer was obtained in 73 hours

Table 1 presents the data of the copolymerization of PABP with MI. It was found that if the content of MI in feed ratio was less than 70%, no detectable copolymers were formed; when the content of MI was greater than 70%, the copolymer was obtained, but the conversion was rather low.

It is well known that the monomer with allylic group may easily conduct the chain transfer [19]. When the concentration of PABP monomer in feed increases, the rate of chain transfer of the growing chain radical to PABP monomer increases simultaneously. A new radicals produced by abstracting of the former a labile allylic hydrogen from the PABP monomer, which is too stable to initiate a new chain. The concentration of growing chain radical, therefore, was lower and lower (Scheme 3), that is why in the higher PABP concentration the copolymerization is difficult to carry out.

Hydrolysis of Copolymer and Characterization of Hydrolyzed Product

In order to obtain a copolymer bearing sulfadiazine as a pendant, deacetylation of copolymer was conducted. As a common procedure, either



Scheme 3.

aqueous solution of NaOH or HCl could be used to remove the acetyl protective group. However for our system, only HCl could be used because the imides of MI might also be hydrolyzed in the aqueous solution of NaOH.

Figure 1 (c) shows a ^{1}H-NMR spectrum of a hydrolyzed copolymer containing 5 mol% of PABP. The complete elimination of acetyl groups and regeneration of the amino groups for copolymer was confirmed by the hydrolysis. The absence of ^{1}H resonance at 2.1 (s, 3H, -CH_3) and 10.3 ppm (s, 1H, -CONH) after hydrolysis clearly indicates no residual acetyl groups left, and a new peak attributed to amino groups appeared at 5.9 ppm. At the same time the signals of protons of phenyl ring shifted from 7.8 [Figure 1(b)] to 6.5 ppm [Figure 1 (c)] due to the influence of amino groups. Based on the evaluation of integration area ratio of methyl to phenyl protons, it could be concluded that all acetyl groups were successfully removed.

CONCLUSION

A new monomer 3-(N-pyrimidin-2-yl-N(-4-acetylaminobenzenesulfonyl)amino-1-propene (PABP) is successfully prepared. It could be copolymerized with maleimide (MI) when MI in feed was greater than 70 mol%. The chain transfer of propagation species to PABP was found. After hydrolysis with 15% HCl, the copolymer bearing sulfadiazine as a pendant is obtained.

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