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POLY(METHYL METHACRYLATE) SUPPORTED HYDROXAMIC ESTERS: A NEW CLASS OF ACYL TRANSFER REAGENTS

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Abstract—Poly(methyl methacrylate) supported hydroxamic esters were prepared and developed as a new class of recyclable solid-phase reagent. The difunctional crosslinking agents employed were divinylbenzene, ethyleneglycol dimethacrylate and *N,N'*-methylene-bis-acrylamide (*N,N'*-MBA). Polymeric hydroxamic esters have been found to be selective in acylating amines and amino acids. When the reactivity of the acyl group attached to the differently crosslinked poly(methyl methacrylate) matrix is compared, it is seen that the acyl transfer functions generated on the *N,N'*-MBA crosslinked poly(methyl methacrylate) are more reactive. The spent reagent can be regenerated to the hydroxamic esters by a simple reaction, without considerable loss in activity. © 1997 Elsevier Science Ltd

INTRODUCTION

Synthetic reagents bound to a polymeric backbone have been widely used as participants in chemical reactions [1–3]. Investigations with various polymeric reagents have revealed that the overall three-dimensional macromolecular structure is decisive in dictating the nature and reactivity of the attached functional groups [4]. With the aim of realising the so called "polymer effects" we have tried to develop an acyl transfer reagent supported on a gel type poly(methyl methacrylate) resin.

A number of acylating reagents have been reported for the acylation of alcohols and amines, and for the synthesis of peptides [5–7]. These reagents were found to activate the carboxyl component for the formation of the amide or peptide bonds.

This paper describes the development of poly(-methyl methacrylate) supported hydroxamic esters, and their use in the synthesis of amides, the reaction conditions used for the acylation of amines, and the effect of the macromolecular support characteristics on the extent of acylation.

EXPERIMENTAL

General

Solvents used were reagent grade and were purified according to literature procedures. Microanalyses were performed at the Regional Sophisticated Instrumentation Centre, I.I.T., Madras. Melting points were determined on a hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 397 spectrometer using KBr pellets. The monomers MMA, DVB, EGDMA were purified by low pressure distillation *N,N'*-Methylene-bis-acrylamide. (*N,N'*-MBA) was recrystallized from ethanol. Methyl methacrylate-divinylbenzene, (**1a**) methyl methacrylate-ethyleneglycol dimethacrylate (**2a**) and methyl methacrylate- *N,N'*-methylene-bis-acrylamide (**3a**) copolymer supports were prepared by adopting procedures reported for parallel cases [8].

Preparation of hydroxamic acid resin (1b, 2b, 3b)

Hydroxylamine hydrochloride (9.2 g) in methanol (15 mL) was neutralized with methanolic potassium hydroxide (10.2 g). The mixture was cooled to 0° and the potassium chloride precipitated was filtered off. Poly(methyl methacrylate) (**1a**, **2a**, **3a**) (10 g), pre-swollen in dichloromethane (20 mL) was then added to the filtrate and stirred for 6 hr. The polymeric potassium hydroxamate was heated to 80° with acetic acid (2 N, 50 mL) for 10 hr to obtain the hydroxamic acid resin. It was filtered at the pump and washed successively with water (20 mL × 5 times), ethanol, methanol and acetone (20 mL × 5 times each). The resin was then dried in vacuum to constant weight. Yield, 10.05 g (**1b**), 10.1 g (**2b**) and 10.2 g (**3b**).

Preparation of hydroxamic ester resin ($1c_1$–$1c_3$, $2c_1$-$2c_3$, $3c_1$-$3c_3$)

The hydroxamic acid resin (**1b**, **2b**, **3b**) (10 g) was suspended in an acetonitrile–chloroform mixture (1:1 v/v, 500 mL) and a three-fold molar excess of acyl halide (acetyl chloride, benzoyl chloride or *p*-nitrobenzoyl chloride) was added to the suspension. Pyridine (5 mL) was added and the mixture was stirred for 8 hr. The reaction mixture was filtered at the pump to collect the resin particles, washed with acetonitrile, hot water, ethanol, methanol and acetone (20 mL × 2 min × 3 times each) and dried in vacuum. Yield, 10.2 g (**1c$_1$**), 10.3 g (**1c$_2$**)), 10.5 g (**1c$_3$**), 10.3 g (**2c$_1$**), 10.5 g (**2c$_2$**), 10.6 g (**2c$_3$**), 10.5 g (**3c$_1$**), 10.6 g (**3c$_2$**) and 10.8 g (**3c$_3$**).

Acyl transfer reactions using poly(methyl methacrylate) bound hydroxamic esters

The poly(methyl methacrylate) based hydroxamic ester (1 mmol) was suspended in chloroform (20 mL) and the amine (0.5 mmol) added to it. The mixture was stirred at room temperature for a definite period when maximum conversion was observed as indicated by TLC. The reaction

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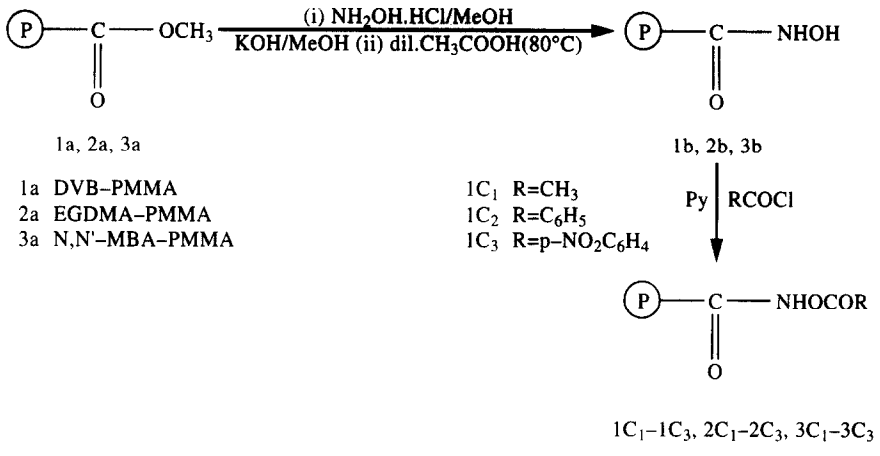


Scheme 1. Preparation of poly(methyl methacrylate) based hydroxamic esters.

mixture was filtered and washed with chloroform. To the filtrate, dil HCl (25 mL) was added and the mixture was shaken well to remove the excess amine. The organic layer was collected and chloroform was evaporated to obtain the amide.

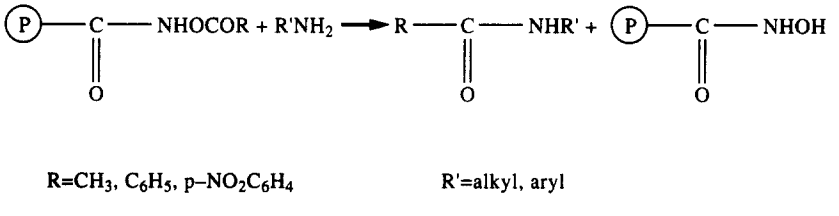
RESULTS AND DISCUSSION

Synthesis of poly(methyl methacrylate) bound hydroxamic ester resins

Two per cent crosslinked poly(methyl methacrylate) was used as the support. The various crosslinking agents used were DVB, EGDMA and *N,N'*-MBA. Copolymers of methyl methacrylate with DVB (**1a**) and EGDMA (**2a**) were prepared by suspension polymerization of the monomer mixture in water at 80° using benzoyl peroxide as the initiator. *N,N'*-MBA crosslinked poly(methyl methacrylate) (**3a**) was prepared by a solution polymerization technique. Benzoyl peroxide was used as the initiator [8]. Ethanol was used as the homogenising medium. Synthesis of poly(methyl methacrylate) bound hydroxamic ester involves a series of polymer analogous reactions (Scheme 1). The methyl ester group of the polymer was easily converted to the hydroxamic acid function by reaction with hydroxylamine [9]. For this, hydroxylamine hydrochloride was first neutralized with alcoholic potassium hydroxide and the neutral hydroxylamine was reacted with the polymer. The formation of hydroxamic acid was supported by elemental analysis and the IR spectrum. When the ester group was converted to the hydroxamic acid function, the IR band corresponding to the ester group [1700 cm^{-1} ($C{=}O_{str}$)] disappeared and those corresponding to NH—OH [3400 cm^{-1} ($N{-}H_{str}$), 3500 cm^{-1} ($O{-}H_{str}$)] were found. The hydroxyl group capacity was determined by the acetylation method using acetylating mixture [10]. The nitrogen content of hydroxamic acid was estimated by CHN analysis. The hydroxamic acid resin was converted to the corresponding ester by treating the former with acyl halide (CH_3COCl, C_6H_5COCl, p-$NO_2C_6H_4COCl$) in a mixture of acetonitrile and chloroform (1:1 v/v) in the presence of pyridine. The formation of poly(methyl methacrylate) supported hydroxamic esters was supported by elemental analysis and estimation of the acyl group capacity [11]. Disappearance of the absorption band due to the —OH function and the appearance of a new carbonyl band at 1690 cm^{-1} in the IR spectrum also supported the formation of an hydroxamic benzoate function. The analytical details of the prepared reagents are given in Table 1.

Poly(methyl methacrylate) bound hydroxamic esters on reaction with amines transfer their acyl group to the amine forming an amide (Scheme 2). In order to check the acylating ability of the hydroxamic ester resin, the resin was first treated with the amine in a 2:1 molar ratio, in solvents like chloroform at room temperature. The reaction was monitored by TLC. After the reaction, the mixture was filtered, the resin was washed with the solvent, the filtrate and washings were collected together which on evaporation afforded the product. In cases where complete conversion of the amine was not possible, the excess amine was extracted with dil HCl. The products were recrystallized and characterized by comparison with authentic samples (IR and melting point).

The acylation studies were tried on different amines using the poly(methyl methacrylate) supported



Scheme 2. Acyl transfer reaction of poly(methyl methacrylate) based hydroxamic ester resins.

Table 1. Analytical details of poly(methyl methacrylate) bound hydroxamic acids and hydroxamic esters

Resin	N[%][a]	Functional group capacity (meq/g)
1b	4.1	2.9[b]
2b	4.7	3.3[b]
3b	5.5	3.9[b]
$1c_1$	3.6	2.5[c]
$1c_2$	4.3	3.0[c]
$1c_3$	9.4	3.3[c]
$2c_1$	4.1	2.9[c]
$2c_2$	4.5	3.2[c]
$2c_3$	10.2	3.6[c]
$3c_1$	4.7	3.3[c]
$3c_2$	5.2	3.7[c]
$3c_3$	11.5	4.0[c]

[a]Determined by CHN analysis.
[b]Determined by acetylation method.
[c]Determined by titrimetric method.

Table 3. Acyl transfer reactions using EGDMA crosslinked poly(methyl methacrylate) bound hydroxamic esters

Number	Amine	Solvent	Duration[a] (hr)	Yield (%) $2c_1$	$2c_2$	$2c_3$
1	aniline	$CHCl_3$	4.0	58	69	82
2	*o*-toluidine	$CHCl_3$	4.5	62	74	87
3	*m*-toluidine	$CHCl_3$	4.5	60	70	84
4	*p*-toluidine	$CHCl_3$	4.5	61	72	86
5	*m*-chloroaniline	$CHCl_3$	4.5	49	60	75
6	*p*-chloroaniline	$CHCl_3$	4.5	50	62	78
7	*o*-aminophenol	$CHCl_3$	4.5	54	66	81
8	glycine	dioxan: water (1:1)	4.5	51	60	76
9	methylamine	dioxan	4.5	67	80	90
10	2,4-dimethylaniline	$CHCl_3$	4.0	52	63	79
11	2,6-dimethylaniline	$CHCl_3$	4.0	54	65	81

[a]Time for maximum conversion; temperature, 30°C.

hydroxamic esters as acylatings agents. The details of acylation reactions are given in Tables 2–4. The percentage yield of the products given in the table is the actual percentage of isolated pure products. The resins do not react with hydroxyl or carboxyl groups, therefore selective acylation is possible in the case of multifunctional amino compounds. In the case of aminophenols, only the amino groups are acylated. The resin did not react with ethanol to give ethyl benzoate and on reaction with glycine gave only the benzoyl glycine.

The acylation studies revealed that the extent of acyl group transfer was very much dependent on the structure of the substrates. Acylation of aniline using *N,N'*-MBA crosslinked poly(methyl methacrylate) bound hydroxamic benzoate gave 74% yield, whereas *o*-toluidine gave 79% yield. Electron releasing groups like CH_3 increase the nucleophilicity of the substrate. Thus the extent of acyl group transfer increased with the increase in nucleophilicity of the substrate. The benzoylation of *p*-chloroaniline using *N,N'*-MBA crosslinked poly(methyl methacrylate) bound hydroxamic benzoate gave a lower yield of 69% compared to aniline. For aliphatic amines like methyl amine, the amide yield was higher.

Acylation of aniline using poly(methyl methacrylate) supported hydroxamic *p*-nitrobenzoate (**$1c_3$, $2c_3$** and **$3c_3$**) gave a higher yield compared to that of hydroxamic benzoate (**$1c_2$, $2c_2$** and **$3c_2$**) and hydroxamic acetate resins (**$1c_1$, $2c_1$** and **$3c_1$**). In the case of *N,N'*-MBA crosslinked poly(methyl methacrylate) resins, hydroxamic benzoate resin gave 74% yield, the corresponding hydroxamic acetate gave only 62% and hydroxamic *p*-nitrobenzoate gave 87%. Thus the *p*-nitrobenzoyl group is found to be a better leaving group.

The above discussion reveals that, the nature of the crosslinking agent on the polymer has a definite influence on the extent of functional group conversions and also on the reactivity of the bound acyl group. When the reactivity of the acyl group attached to the differently crosslinked poly(methyl methacrylate) matrix is compared along the three series, viz., DVB, EGDMA and *N,N'*-MBA crosslinked systems, it is seen that the acyl transfer functions generated on the *N,N'*-MBA crosslinked poly(methyl methacrylate) are more reactive than EGDMA and DVB crosslinked systems. Acyl transfer reagents derived from EGDMA crosslinked PMMA supports were found to be superior to those based on DVB crosslinked PMMA supports in terms of reactivity. The acyl group capacity of *N,N'*-MBA crosslinked PMMA supported hydroxamic benzoate was 3.7 meq/g and the extent of benzoylation of aniline using this resin was 74%, whereas the capacity of DVB crosslinked PMMA supported hydroxamic benzoate was 3 meq/g and the extent of conversion of aniline using this resin was 60%. The capacity of EGDMA crosslinked poly(methyl methacrylate) supported hydroxamic benzoate was 3.2 meq/g and the extent of benzoylation using this resin was 69%.

Table 2. Acyl transfer reactions using DVB crosslinked poly(methyl methacrylate) bound hydroxamic esters

Number	Amine	Solvent	Duration[a] (hr)	Yield (%) $1c_1$	$1c_2$	$1c_3$
1	aniline	$CHCl_3$	4.0	53	60	72
2	*o*-toluidine	$CHCl_3$	4.5	56	64	78
3	*m*-toluidine	$CHCl_3$	4.5	53	62	76
4	*p*-toluidine	$CHCl_3$	4.5	55	63	74
5	*m*-chloroaniline	$CHCl_3$	4.5	45	50	54
6	*p*-chloroaniline	$CHCl_3$	4.5	47	52	57
7	*o*-aminophenol	$CHCl_3$	4.5	50	55	63
8	glycine	dioxan: water (1:1)	4.5	47	50	55
9	methylamine	dioxan	4.0	62	74	80
10	2,4-dimethylaniline	$CHCl_3$	4.0	49	55	59
11	2,6-dimethylaniline	$CHCl_3$	4.0	52	58	63

[a]Time for maximum conversion; temperature, 30°C.

Table 4. Acyl transfer reactions using *N,N'*-MBA crosslinked poly(methyl methacrylate) bound hydroxamic esters

Number	Amine	Solvent	Duration[a] (hr)	Yield (%) $3c_1$	$3c_2$	$3c_3$
1	aniline	$CHCl_3$	4.0	62	74	87
2	*o*-toluidine	$CHCl_3$	4.5	66	79	94
3	*m*-toluidine	$CHCl_3$	4.5	63	76	90
4	*p*-toluidine	$CHCl_3$	4.5	65	77	92
5	*m*-chloroaniline	$CHCl_3$	4.5	52	64	79
6	*p*-chloroaniline	$CHCl_3$	4.5	55	69	82
7	*o*-aminophenol	$CHCl_3$	4.5	57	70	85
8	glycine	dioxan: water (1:1)	4.5	54	66	80
9	methylamine	dioxan	4.5	72	85	97
10	2,4-dimethylaniline	$CHCl_3$	4.0	57	69	83
11	2,6-dimethylaniline	$CHCl_3$	4.0	61	73	85

[a]Time for maximum conversion; temperature, 30°C.

Table 5. Effect of solvents on acylation of aniline using poly(methyl methacrylate) bound hydroxamic esters

Resin	Yield (%) of anilide formed in						
	$CHCl_3$	CH_2Cl_2	CCl_4	CH_3CN	THF	C_6H_6	Dioxan
$1c_1$	53	56	43	60	56	48	38
$1c_2$	60	64	50	70	67	55	46
$1c_3$	72	74	57	80	77	60	50
$2c_1$	58	64	50	70	67	54	48
$2c_2$	69	76	60	80	77	63	54
$2c_3$	82	89	69	93	87	75	65
$3c_1$	62	73	76	79	76	60	48
$3c_2$	74	86	65	88	85	69	60
$3c_3$	87	94	76	97	93	80	72

[a]Substrate to resin ratio, 1:2; temperature 30°C; time, 4 hr.

Table 6. Effect of temperature on acylation of aniline using poly(methyl methacrylate) bound hydroxamic esters

Resin	Yield (%) of anilide formed at					
	10°	20°	30°	40°	50°	60°
$1c_1$	45	47	53	56	60	65
$1c_2$	50	55	60	66	72	80
$1c_3$	65	67	72	76	79	82
$2c_1$	53	55	58	60	64	70
$2c_2$	63	66	69	73	77	82
$2c_3$	74	78	82	86	89	91
$3c_1$	55	58	62	65	69	72
$3c_2$	64	70	74	77	80	85
$3c_3$	80	84	87	90	92	94

[a]Substrate to resin ratio, 1:2; solvent, chloroform; time, 4 hr.

The increased reactivity of the *N,N'*-MBA crosslinked poly(methyl methacrylate) supported hydroxamic esters can be ascribed to the attainment of the optimum hydrophilic/hydrophobic balance of the polymer matrix. The comparable reactivity of EGDMA crosslinked PMMA bound acyl transfer reagents can be attributed to the increased flexibility of the polymer support and also to the compatibility of the supported reagent with the substrate and solvent.

Effect of reaction conditions and extent of acyl transfer

The acylation reaction using poly(methyl methacrylate) supported hydroxamic esters were found to be affected by the nature of the solvent, temperature, reaction period and effective concentration of the reagent function. It has been observed that only when there is an effective interaction between the reagent function, the substrate and the reaction medium, will reaction take place with a reasonable degree of functional group conversions.

Effect of solvent

A major factor influencing the efficiency of the polymer supported reactions is the type of solvent used for the reaction. In order to investigate the effect of the nature of the solvent on the reactivity of acylating reagents, an acyl transfer reaction with aniline was conducted using poly(methyl methacrylate) supported hydroxamic esters in a 1:2 molar ratio in different solvents with varying polarity. The extent of conversion after 4 hr at 30° was calculated. The studies reveal that acetonitrile is the most effective solvent. Solvents which are capable of swelling the polymer network, which are also able to dissolve the low molecular weight substrates are found to be suitable for carrying out the acylation reaction. The percentage yield of anilide obtained using the different resins are given in Table 5.

Effect of temperature

The acylation of aniline with polymer bound hydroxamic esters in a 1:2 molar ratio was carried out in chloroform for 4 hr at different temperatures ranging from 10 to 60°. The results are given in Table 6.

It was found that as the temperature was increased, the percentage yield of anilide obtained increased gradually. The higher reactivity of polymeric acyl transfer reagents at higher temperature may be due to the attainment of the required activation energy by the molecules. As the number of molecules with required activation energy increases, the acyl group transfer capacity also increases.

Duration of reaction

Acylation of aniline was carried out at room temperature in chloroform using PMMA bound hydroxamic esters in a 1:2 molar ratio. The percentage yield of the product obtained was determined at fixed time intervals. The results are given in Table 7.

The reaction of aniline with poly(methyl methacrylate) bound hydroxamic esters after a period of 4 hr gave maximum yield of anilides. After that, on further increase in reaction time, the amount of anilide was found to decrease slightly. This may possibly be due to the physical adsorption of the anilide on the spent resin.

Effect of molar ratio

Acylation reactions using PMMA bound hydroxamic esters were found to be dependent on the effective concentration of the reagent function. To study the dependence of the reactivity of acylating function on their effective concentration, the acylation reaction with aniline was conducted at different reagent to substrate ratios in chloroform at 30°. The relative concentrations studied were 1:1, 2:1, 3:1, 4:1, and 5:1. When the molar equivalent was used, the reaction did not go to completion in any case, irrespective of the duration of reaction. The results are given in Table 8. The results revealed that with an increased resin to amine ratio, there was a corresponding increase in the percentage yield of anilide formed. It was found that the percentage of anilide formed was almost doubled

Table 7. Acylation of aniline using poly(methyl methacrylate) bound hydroxamic esters at various time intervals

Resin	Conversion (%) after					
	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
$1c_1$	30	39	44	53	51	49
$1c_2$	35	44	52	60	58	55
$1c_3$	40	52	61	72	70	68
$2c_1$	30	39	44	58	55	53
$2c_2$	39	47	54	69	66	64
$2c_3$	50	64	72	82	80	77
$3c_1$	35	42	50	62	60	58
$3c_2$	40	50	60	74	72	70
$3c_3$	50	62	73	87	85	83

[a]Substrate to resin ratio, 1:2; solvent, chloroform; temperature, 30°C.

Table 8. Acylation of aniline using poly(methyl methacrylate) bound hydroxamic esters with different resin:amine ratio[a]

Resin	Conversion (%) when the molar ratio is				
	1:1	2:1	3:1	4:1	5:1
$1c_1$	28	53	57	60	64
$1c_2$	33	60	64	67	70
$1c_3$	38	72	74	77	80
$2c_1$	30	58	60	63	66
$2c_2$	39	69	72	75	77
$2c_3$	44	82	85	87	90
$3c_1$	35	62	65	68	70
$3c_2$	38	74	77	80	83
$3c_3$	45	87	90	92	95

[a]Solvent, chloroform; temperature, 30°C; time, 4 hr.

Table 9. Regeneration of the *N,N'*-MBA crosslinked poly(methyl methacrylate) based hydroxamic benzoate resin

No. of cycles	Benzoyl group capacity (meq/g)	Isolated yield[a]
1	3.7	74
2	3.6	73
3	3.6	73
4	3.5	71
5	3.5	71

[a]Acylation of aniline to benzanilide in chloroform at room temperature. Yield noted after 4 hr. Aniline to resin ratio, 1:2.

when the resin to amine ratio was changed from 1:1 to 5:1.

Recycling of the spent reagents

Regenerability is a major advantage of polymer supported reagents. It was observed that *N,N'*-MBA crosslinked poly(methyl methacrylate) supported hydroxamic benzoate could be recycled without appreciable loss in capacity or activity. The polymeric by-product obtained after the acyl group transfer reaction could be converted to the original hydroxamic benzoate resin by simple treatment with benzoyl chloride. The regenerated resins obtained showed almost identical reactivity as that of the original resins. The details are given in Table 9.

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