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Acetoacetoxy ethyl methacrylate (AAEM) resin, a new scavenger for primary amines in the presence of secondary amines

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Abstract

Preliminary results on a new type of polymer scavenger, acetoacetoxy ethyl methacrylate (AAEM) resin, are reported. AAEM resin can selectively remove primary amines in the presence of secondary amines. Its application in a solution library synthesis is demonstrated.

Keywords: combinatorial chemistry; reductive alkylation; polymer scavenger; amines.

Over the past few years, the exploration and utilisation of combinatorial chemistry as a pharmaceutical drug discovery technology has rapidly evolved. The field of combinatorial chemistry has expanded to include not only solid- and solution-phase methods for expedited compound synthesis, but also hybrid approaches which combine the purification advantages of solid-phase synthesis with the flexibility of solution-phase synthesis.[1] Inherent in any approach to produce chemical libraries is the need to rapidly purify, isolate, and manipulate chemical library members during their preparation. Polymer scavenging reagents[2,3] have thus emerged as useful tools for combinatorial synthesis, specifically, for solution-phase chemical library synthesis.

Secondary amines are important pharmacophores in many biologically active compounds. They are often prepared by reductive alkylation of primary amines with aldehydes or ketones,[4] although overalkylation readily occurs.[5] In order to overcome overalkylation, excess primary

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amine is usually used, thus, generating the problem of how to purify the secondary amine obtained or to remove selectively the primary amine in the presence of the secondary. Traditional distillation and chromatographic methods are unsuitable for chemical library synthesis, and thus it is desirable to develop and use polymer scavenging reagents for selective removal of the primary amines in the presence of the secondary.

In this area, benzaldehyde resins (Fig. 1, **A**) have been reported,[2] but are not particularly stable and may be oxidised in air. Herein, we wish to report preliminary results on a new kind of polymer, acetoacetoxy ethyl methacrylate (AAEM) resin (3.0 mmol/g, available from Avecia Ltd) (Fig. 1, **B**) as a scavenger for primary amines in the presence of secondary amines.

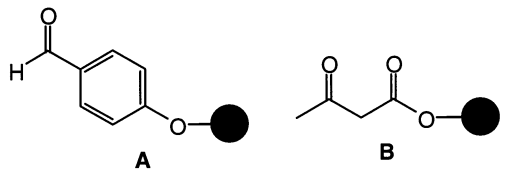


Figure 1. Benzaldehyde resin (**A**) and acetoacetoxy ethyl methacrylate (AAEM) resin (**B**)

In order to optimise the reaction conditions, two pairs of amines: benzylamine ($BnNH_2$)/*N*-benzylmethylamine (BnNHMe) and benzylamine/dibenzylamine were selected as model compounds to test the new AAEM resin. HPLC was used as the analytical tool.[6] The two pairs of amines were treated with AAEM resin in different solvents, 2-propanol (2-PrOH) or tetrahydrofuran (THF) at different temperatures.[7] The results are shown in Figs. 2 and 3. The primary amine, benzylamine, was removed at ambient temperature, although the rate of removal was accelerated at slightly elevated temperature (40°C) (Fig. 2). The secondary amines, *N*-benzylmethylamine or dibenzylamine showed little loss under the same conditions even at higher temperature (40°C) (Fig. 3). 2-Propanol was much more effective than tetrahydrofuran. These results indicated that AAEM resin had high selectivity for the primary amine, benzylamine.

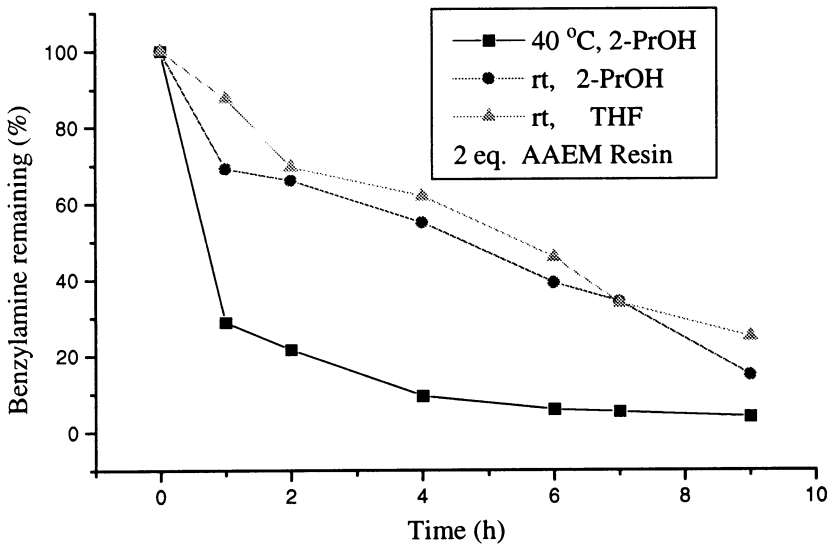


Figure 2. Removal of benzylamine

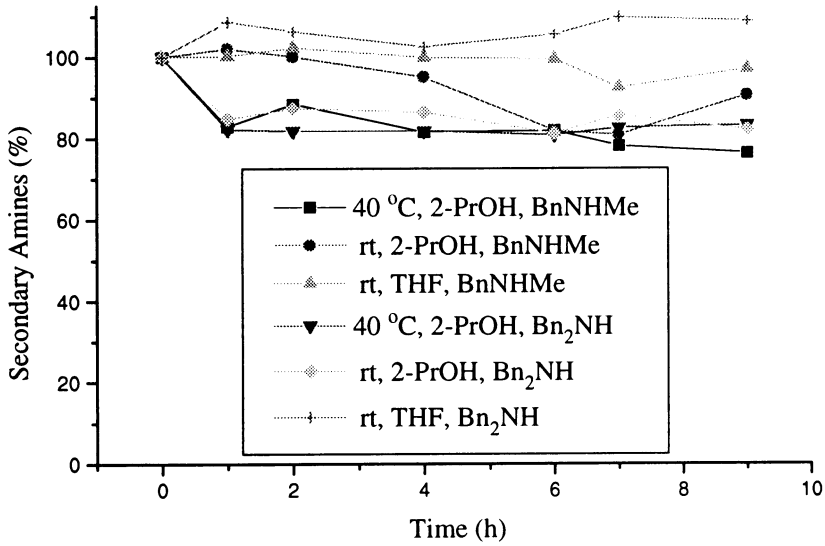


Figure 3. Removal of secondary amines

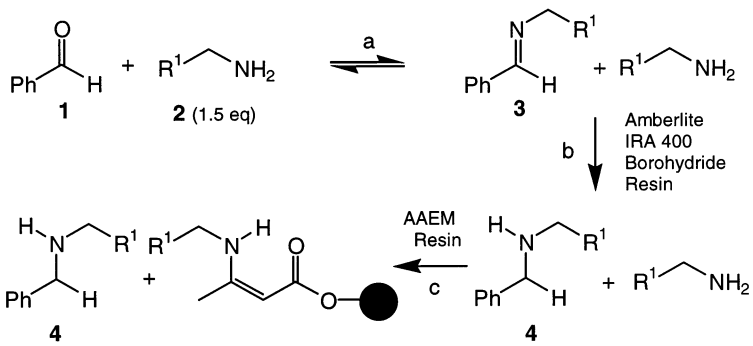
The data in Table 1 show the effect solvent has on the removal of benzylamine from a mixture of benzylamine and *N*-benzylmethylamine. Benzylamine could be selectively removed in all the solvents utilised. 2-Propanol gave much better results than methanol, while a mixture of 2-propanol and tetrahydrofuran or dichloromethane (DCM) gave slightly better purities for the secondary amine, *N*-benzylmethylamine.

Table 1
Effects of solvent on the removal of $BnNH_2$ from a mixture of $BnNHMe/BnNH_2$[a]

Solvents	Purity (%, HPLC)[b]	Recovery of BnNHMe (%)
MeOH	93	41
MeOH/DCM (1:1)	95	71
2-PrOH	96	72
2-PrOH/DCM (1:1)	100	65
2-PrOH/THF (1:1)	100	69

[a] Conditions. Solvent: 4.0 ml; 2 molar equiv. of AAEM resin relative to benzylamine; time: 48 hours; room temperature; $BnNH_2/BnNHMe$ (80 mg/140 mg).
[b] Ratio of $BnNHMe/(BnNHMe+BnNH_2)$.

Having obtained these results, secondary amines were prepared by reductive alkylation, as shown in Scheme 1.[8] Benzaldehyde was selected as the carbonyl component, while the primary amines used were benzylamine, 2-furylmethylamine, 2-phenylethylamine, 1-naphthylmethylamine, 2,2-diphenylethylamine and diphenylmethylamine. The results obtained are given in Table 2.



Scheme 1. (a) 2-PrOH or MeOH, 2 h; (b) 2-PrOH or MeOH, 24 h, Amberlite IRA 400 borohydride resin (2 equiv.); (c) 2-PrOH/THF or MeOH/CH_2Cl_2 (1:1, v/v), 36 h, AAEM resin (2 equiv.)

Table 2
Results of reductive alkylation

R^1	Solvents		Compound	Purity (%)	Yield (%)
	Step a+b	Step c[a]			
Phenyl	2-PrOH	2-PrOH/THF	3	100[b]	60
2-Furyl	2-PrOH	2-PrOH/THF	3	100[b]	68
Benzyl	2-PrOH	2-PrOH/THF	3	100[b]	70
1-Naphthyl	2-PrOH	2-PrOH/THF	3	100[b]	56
Benzhydryl	2-PrOH	2-PrOH/THF	3	98[b]	54
Diphenyl	2-PrOH	2-PrOH/THF	3	97[b]	63
Phenyl	MeOH	MeOH/DCM	4	100[c]	81
2-Furyl	MeOH	MeOH/DCM	4	100[b]	88
Benzyl	MeOH	MeOH/DCM	4	100[c]	87
1-Naphthyl	MeOH	MeOH/DCM	4	100[b]	72
Benzhydryl	MeOH	MeOH/DCM	4	93[b]	69
Diphenyl	MeOH	MeOH/DCM	4	87[b]	80

[a] Ratio 1/1 (v/v).
[b] Purity obtained by ^1H NMR.
[c] Purity obtained by HPLC.

Initially, 2-propanol and tetrahydrofuran were used as solvents, benzaldehyde being converted to the corresponding imines (**3**) with the primary amines. However, polymer supported borohydride[9] failed to reduce these imines (**3**) to the corresponding secondary amines; the starting imines (**3**) were instead recovered. It is known[10] that the rate of reduction of carbonyl compounds, with sodium borohydride, is solvent dependent with reductions in methanol being much more rapid than in 2-propanol. Thus, methanol and dichloromethane were chosen as solvents in the second test. In this solvent system benzaldehyde yielded the corresponding pure secondary amines (**4**) by reductive amination, as shown in Scheme 1. It is very interesting that the polymer supported borohydride showed such high selectivity for imines in these different solvents.

In summary, we have shown that the new acetoactoxy ethyl methacrylate (AAEM) resin can be used as a scavenging reagent for primary amines in the presence of secondary amines. Its application in library synthesis has been demonstrated.

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6. HPLC System: Hewlett Packard Chemstation: HP series 1100. Column: Prodigy 5μ ODS3, 150×3 mm, Phenomenex; UV Detector: 254 nm. Mobile phase: gradient from water (0.1% TFA) to MeCN (0.042% TFA) in 20 min. Flow rate: 0.5 ml/min. Benzylamine (6.9 min), *N*-benzylmethylamine (7.2 min) and dibenzylamine (9.7 min).
7. Procedure: To a solution of 1.5 mmol of benzylamine and 2.6 mmol of secondary amine (*N*-benzylmethylamine or dibenzylamine) in 8.0 ml of solvent (see notes in Figures) was added 1.0 g (3.0 mmol) of AAEM resin at different temperatures. A sample (10 μl) of the solution was taken from the suspension and diluted to 1.0 ml of acetonitrile. The sample was analysed by HPLC.
8. Procedure: To a solution of 0.5 mmol of benzaldehyde in 1.5 ml of solvent (2-PrOH or MeOH) was added 0.8 mmol of benzylamine. The resulting solution was shaken for 2 h at room temperature to allow for imine formation, and then 0.4 g of Amberlite IRA 400 borohydride resin (2.5 mmol $NaBH_4$/g resin, 1.0 mmol) was added to the solution. The resulting suspension was shaken for 24 h at room temperature. 1.5 ml of solvent (THF or dichloromethane) was added. 0.2 g of AAEM resin was added to the suspension. The resulting suspension was shaken for 36 h at room temperature. The resin was filtered off and the solution was evaporated to give the corresponding products (see Table 2).
9. Amberlite IRA 400 borohydride exchange resin, purchased from Aldrich Chemical Company.
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