Ketoester methacrylate resin, secondary amine clean-up in the presence of primary amines

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A ketoester resin was developed as the basis for a selective scavenger for primary amines in the presence of secondary amines. The utility of the scavenger was demonstrated with a range of reductive amination chemistries with both mono- and diamines. The resin's specificity is based on the removal of the primary amines *via* their enamines.

Introduction

Combinatorial chemistry has emerged as a powerful tool for the discovery of novel pharmaceutical agents and has revolutionized medicinal chemistry. It is generally divided into two tactical domains: solid phase and solution phase synthesis. In the solid phase synthesis approach, the solid support provides an inherently simple means for the separation of the desired product from excess reactants by simple filtration and rinsing of the solid-supported product with solvent. When the final product is cleaved from the solid support it is often found in a substantially pure form.

However, short syntheses are often simply more practical in solution than on a solid support when an efficient purification strategy exists since no resin attachment and cleavage reactions are required. Scavenging resins and reagents [1–10] that have been around for many years thus offer the potential of a new approach to parallel and efficient purification methodologies.

The general concept involves the addition of one or more solid-supported scavengers which selectively react with impurities or excess starting materials present in the reaction mixture on the basis of chemical compatibility. This process facilitates the rapid recovery of the product without the need for time-consuming chromatography. The resin bound impurity is simply removed by a subsequent filtration step completing the separation and leaving a solution of the desired product with enhanced purity. This methodology combines the purification and mass action advantages of solid phase synthesis with the flexibility of solution phase synthesis.

Secondary amines, like primary amines, are amongst the most popular class of building blocks for the library synthesis of organic molecules. They are used in a broad range of synthetic reactions and in the synthesis of nitrogen-containing pharmaceutical and agricultural products. Although over-alkylation occurs,[11] reductive alkylation of primary amines with aldehydes or ketones [12–16] is one of the most useful methodologies in library syntheses of secondary amines. Excess primary amines are usually used to reduce the over-alkylation issue, 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 was desirable to develop polymer scavenging reagents for the selective removal of the primary amines in the presence of the secondary.

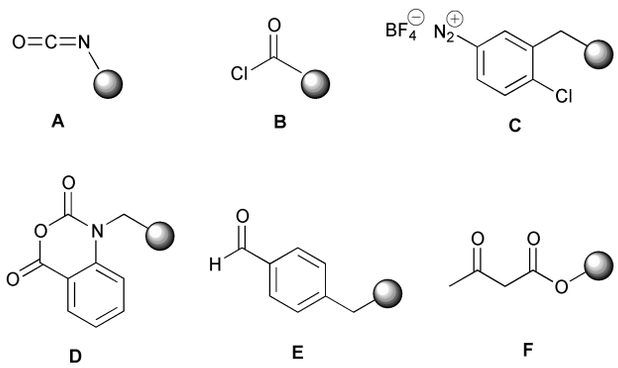

Fig. 1 Some polymer based scavengers for amine removal.

Although several reports have described the removal of amines using resins, which contain electrophilic functionalities, such as isocyanates [1,8] (Fig. 1, **A**), carboxylic acid chlorides [1] (Fig. 1, **B**), diazonium species [17] (Fig. 1, **C**) or isatoic† anhydride [18] (Fig. 1, **D**), to date only benzaldehyde resins [1,2] (Fig. 1, **E**) can be used to selectively remove primary amines, *via* imine formation from a mixture of primary and secondary amines. A potential problem with the benzaldehyde resin is that neither the resin itself, due to oxidation in air, nor the imine formed after scavenging primary amines is particularly stable.

Here we wish to report the full details of a ketoester resin (Fig. 1, **F**), designed as a selective scavenger for primary amines in the presence of secondary amines.

Results and discussion

1 Model compounds

Initially, a primary amine, benzylamine ($BnNH_2$) and two secondary amines, *N*-benzylmethylamine (BnNHMe) and dibenzylamine (Bn_2NH) were selected as model compounds to test the new ketoester resin. HPLC was used as the analytical tool. Mixtures of benzylamine with *N*-benzylmethylamine or dibenzylamine were treated with the ketoester resin in different solvents at different temperatures. The results are shown in Figs. 2 and 3. The purities of the secondary amines increased,

† The IUPAC name for isatoic acid is 2-(carboxyamino)benzoic acid.

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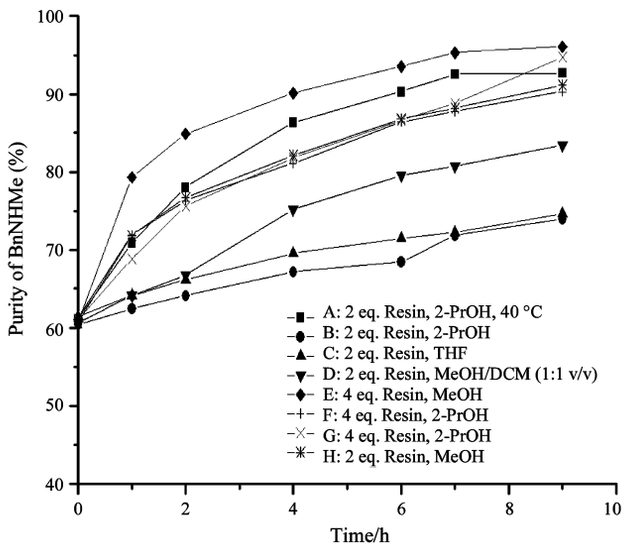


Fig. 2 Removal of $BnNH_2$ in the presence of BnNHMe.

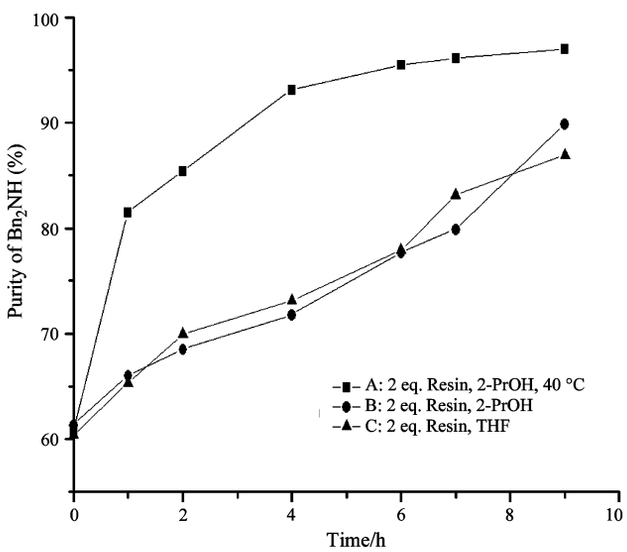


Fig. 3 Removal of $BnNH_2$ in the presence of Bn_2NH.

i.e. the primary amine, benzylamine, was removed. As expected, the rates of removal of benzylamine were faster at higher temperature (40 °C) and when a greater excess of resin was used. In less than 9 hours, the purities of the secondary amines reached >90% (40 °C and 4 eq. resin used). At lower molar ratios of resin (2 eq.), the purities went to >91% after 30 hours. These results indicated that the ketoester resin had high selectivity for primary amines over secondary amines.

2 Application of the ketoester resin in the library synthesis of secondary amines

After studying model compounds, the ketoester resin was used in a library synthesis of secondary amines by reductive alkylation as shown in Scheme 1. Benzaldehyde, pentan-2-one and 3,4-dimethoxyphenyl methyl ketone were selected as the carbonyl compounds, while the primary amines used were 2-furylmethylamine, benzylamine, 2-(aminomethyl)pyridine, diphenylmethylamine, 2,2-diphenylethylamine, 2-phenylethylamine, 1-naphthylmethylamine, along with two primary diamines, 1,4-diaminocyclohexane and *p*-xylylenediamine [1,4-bis(aminomethyl)benzene] (Fig. 4). The results obtained are presented in Table 1, and show that the secondary amines were obtained in high purities and good yields.

The alkylated diamines were also obtained in high purities as shown in Table 2, although the yields were less impressive.

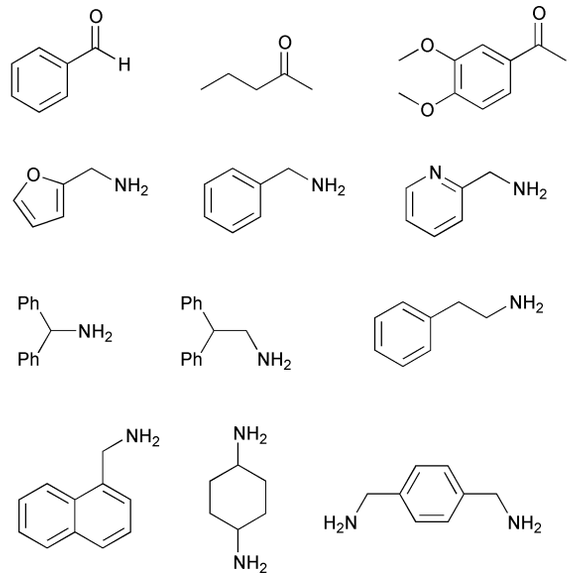
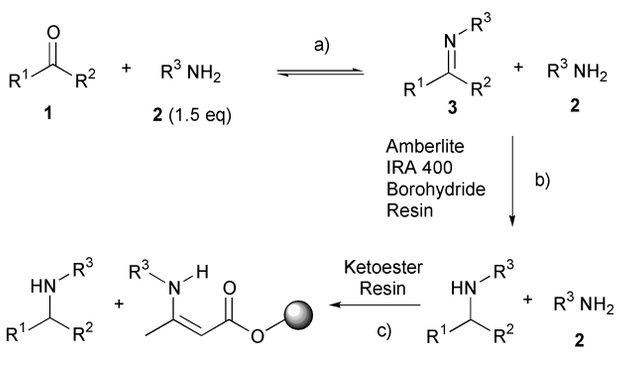


Fig. 4 Carbonyl compounds and primary amines used in reductive alkylation library synthesis.

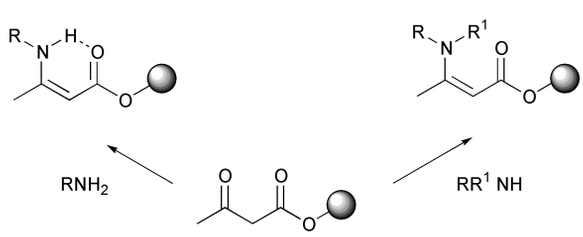


Scheme 1 a) MeOH, 2 h; b) MeOH, 24 h, Amberlite IRA 400 borohydride resin (2 eq.); c) MeOH–CH_2Cl_2 (1 : 1, v/v), 36 h, ketoester resin (2 or 3 eq.).

With 3,4-dimethoxyphenyl methyl ketone, no secondary amines were produced presumedly because of its low reactivity in the imine-forming step, only 1-(3,4-dimethoxyphenyl)-ethanol was isolated.

3 Structure of the resin scavenged primary amines

Why is the new ketoester resin able to selectively remove primary amines in the presence of the secondary? One of the reasons is the higher stability of the enamino ester derived from the primary amine compared to the one derived from the secondary due to formation of an intramolecular H-bond (Scheme 2).



Scheme 2 Possible structures of the resin scavenged primary and secondary amines.

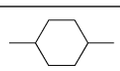
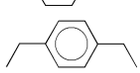
A simple model compound, formed by reaction of methyl acetoacetate with one equivalent of benzylamine in methanol to give methyl 3-benzylaminobut-2-enoate in 95% yield

Table 1 Results of reductive alkylation

Compound	R^1	R^2	R^3	Purity (%)	Yield (%)
4a	Ph	H	Furan-2-ylmethyl	>95[b]	88
4b	Ph	H	Benzyl	100[a]	81
4c	Ph	H	Pyridin-2-ylmethyl	>95[b]	86
4d	Ph	H	Benzhydryl	87[b]	80
4e	Ph	H	2,2-Diphenylethyl	93[b]	69
4f	Ph	H	Phenylethyl	100[a]	87
4g	Ph	H	Naphthalen-1-ylmethyl	>95[b]	72
4h	Pr	Me	Furan-2-ylmethyl	>95[b]	69
4i	Pr	Me	Benzyl	>95[b]	83
4j	Pr	Me	Pyridin-2-ylmethyl	100[a]	87
4k	Pr	Me	Benzhydryl	74[b]	68
4l	Pr	Me	2,2-Diphenylethyl	81[b]	69
4m	Pr	Me	Phenylethyl	95[b]	85
4n	Pr	Me	Naphthalen-1-ylmethyl	86[b]	71

[a] Purity obtained by HPLC. [b] Purity obtained by ^{1}H NMR.

Table 2 Reductive alkylation of primary diamines

Compounds (**5** = Bn–NH–Z–NH–Bn)	Z	Purity[a] (%)	Yield (%)
5a		86	38
5b		>95	41

[a] Purity obtained by ^{1}H NMR.

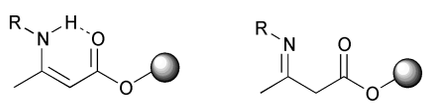
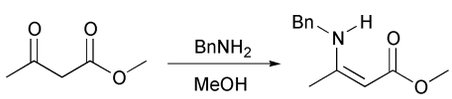


Fig. 5 Two possible structures of the resin trapped primary amines.



Scheme 3 Preparation of methyl 3-benzylaminobut-2-enoate in solution.

(Scheme 3), was examined by ^{13}C NMR and compared with the equivalent resin bound products.

There were two possible forms for the resin once it had reacted with primary amines: one the enamino ester and the other the imino ester (Fig. 5).

Gel-phase ^{13}C NMR of the resins before and after scavenging benzylamine (Fig. 6a and b) was carried out. These two spectra showed that the keto group (200.2 ppm) and the methylene group (50.2 ppm) of the ketoester resin had disappeared and that an enamino group (84.0 and 162.7 ppm) appeared, *i.e.* the stable form is the enamino ester. In addition, Fig. 6a shows that the ketoester resin exists with only a small proportion of the resin in the enol form prior to the scavenging of primary amines.

The ^{13}C NMR spectra of the resins following reaction with benzylamine and the synthetic sample of methyl 3-benzylaminobut-2-enoate (Fig. 6b and 6c) were found to be almost identical. These results show that the product of the primary amine ketoester resin exists exclusively in the enamine form.

In conclusion, it has been shown that the ketoester can be used as a scavenging reagent for primary amines in the presence of secondary amines. Its application in library synthesis has been demonstrated. The structure of the resin scavenged primary amine has been studied. One of the reasons for the selective removal of primary amine in the presence of the secondary is that the enamino ester derived from the primary amine is more stable than the one derived from the secondary amine due to H-bonding considerations.

Experimental

All chemicals were of reagent grade and were used without further purification unless otherwise stated. Infra-red (IR) spectra were recorded on a Bio-Rad Golden Gate FTS 135 spectrophotometer. NMR spectra were recorded on a Bruker AC 300 (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz) spectrometer, a Bruker DPX 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) spectrometer. Mass spectra were recorded on a VG Platform Quadruple Electrospray Ionization spectrometer.

HPLC analyses were performed on an HPLC System: Hewlett Packard Chemstation: HP series 1100. Column: Prodigy 5 ODS3, 150 × 3 mm, Phenomenex; UV detector: 254 nm. Mobile phase: gradient from water (0.1% TFA) to MeCN (0.042% TFA) in 20 minutes. Flow rate: 0.5 ml min^{-1}.

Test of ketoester resin with model compounds

To a solution of benzylamine (1.6 mmol) and secondary amine (*N*-benzylmethylamine or dibenzylamine) (2.5 mmol) in the corresponding solvent (8.0 ml) (see notes in Figs. 2, 3) was added ketoester resin (3.0 mmol g^{-1} resin) (1.0 g) at different temperatures. The solution (10 ml) was taken from the suspension and diluted with acetonitrile (total volume 1.0 ml). The samples were analyzed by RP-HPLC. Benzylamine (6.9 min), *N*-benzylmethylamine (7.2 min) and dibenzylamine (9.7 min). Time = 0 is immediately before the addition of the resin.

Reductive alkylation of primary amines

To a solution of the corresponding carbonyl compound (0.5 mmol) in methanol (1.5 ml) was added the primary amine (0.8 mmol). The resulting solution was shaken for two hours at room temperature to allow imine formation, and then Amberlite IRA 400 borohydride resin (2.5 mmol $NaBH_4$ g^{-1} resin) (0.4 g, 1.0 mmol) was added to the solution. The resulting suspension was shaken for 24 hours at room temperature.

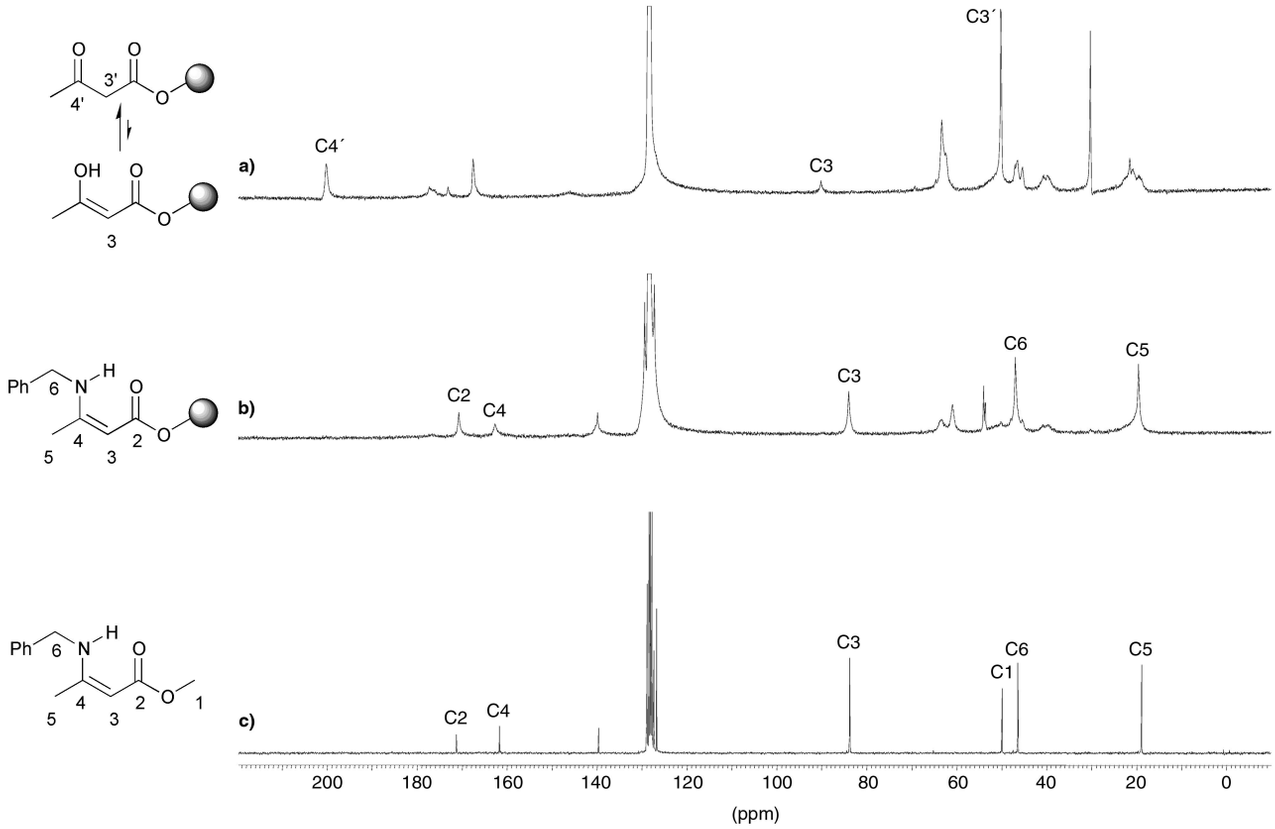


Fig. 6 Comparison of the ^{13}C NMR spectra of the ketoester resin (a) before and (b) after amine addition, and of (c) methyl 3-benzylaminobut-2-enoate.

Dichloromethane (1.5 ml) was then added. Ketoester resin (3.0 mmol g^{-1} resin) (0.2 g, 0.6 mmol) was added to the suspension. The resulting suspension was shaken for 36 hours at room temperature. The resin was filtered off and the solution was evaporated to give the corresponding products (see Tables 1 and 2).

***N*-Benzylfuran-2-ylmethylamine (4a) [4439-53-6]‡.** Yield: 88%. t_R/min: 8.9. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.86 (br, 1H, NH), 3.82 (s, 4H, 2 × CH_2), 6.22 (d, J = 3.0 Hz, 1H, ArH), 6.35 (dd, J = 3.0 and 1.5 Hz, 1H, ArH), 7.35–7.37 (m, 5H, ArH), and 7.40 (d, J = 1.5 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 45.5 (CH_2), 53.0 (CH_2), 107.2, 110.3, 127.2, 128.4 (2), 128.6 (2) and 142.0 (8 × ArCH), 140.0 and 154.0 (2 × ArC). MS (EI), *m*/*z* (%): 188.0 $(M + H)^+$ (100), and 229.2 $(M + 42)^+$ (25).

Dibenzylamine (4b) [103-49-1]. Yield: 81%. t_R/min: 9.7. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.76 (br, 1H, NH), 3.87 (s, 4H, 2 × CH_2), and 7.40–7.42 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 53.4 (2 × CH_2), 127.2 (2), 128.4 (4), and 128.6 (4) (10 × ArCH), 140.5 (2 × ArC). MS (EI), *m*/*z* (%): 198.1 $(M + H)^+$ (100), and 239.2 $(M + 42)^+$ (20).

***N*-Benzylpyridin-2-ylmethylamine (4c) [18081-89-5].** Yield: 86%. t_R/min: 8.5. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.26 (br, 1H, NH), 3.82 (s, 2H, CH_2), 3.90 (s, 2H, CH_2), 7.09–7.14 (m, 1H, ArH), 7.22–7.36 (m, 6H, ArH), 7.59 (td, J = 7.5 and 1.5 Hz, 1H, ArH), and 8.53 (d, J = 5.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 53.6 (CH_2), 54.6 (CH_2), 122.1, 122.5, 127.1, 128.4 (2), 128.5 (2), 136.6 and 149.4 (9 × ArCH), 140.3 and 159.9 (2 × ArC). MS (EI), *m*/*z* (%): 199.1 $(M + H)^+$ (100).

***N*-Benzhydrylbenzylamine (4d) [5669-43-2].** Yield: 80%. t_R/min: 12.7. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.98 (br, 1H, NH), 3.84 (s, 2H, CH_2), 4.96 (s, 1H, CH), and 7.30–7.55 (m, 15H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 52.1 (CH_2), 66.6 (CH), 127.0, 127.1 (2), 127.4 (4), 128.3 (2), 128.5 (2) and 128.6 (4) (15 × ArCH), 140.6 and 144.1 (2) (3 × ArC). MS (EI), *m*/*z* (%): 274.2 $(M + H)^+$ (100), and 348.2 $(M + 75)^+$ (31).

***N*-Benzyl-2,2-diphenylethylamine (4e) [132286-13-6].** Yield: 69%. t_R/min: 12.8. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.56 (br, 1H, NH), 3.30 (d, J = 7.5 Hz, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.30 (t, J = 7.5 Hz, 1H, CH), and 7.22–7.39 (m, 15H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 47.0 (CH_2), 53.9 (CH), 54.0 (CH_2), 126.8 (2), 127.2, 128.25 (4), 128.32 (2), 128.6 (2) and 128.8 (4) (15 × ArCH), 140.2 and 143.0 (2) (3 × ArC). MS (EI), *m*/*z* (%): 288.2 $(M + H)^+$ (100), and 289.3 $(M + 2)^+$ (20).

***N*-Benzylphenethylamine (4f) [3647-71-0].** Yield: 87%. t_R/min: 10.8. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.65 (br, 1H, NH), 2.89–3.00 (m, 4H, 2 × CH_2), 3.87 (s, 2H, CH_2), and 7.25–7.41 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 36.6 (CH_2), 50.8 (CH_2), 54.1 (CH_2), 126.4, 127.1, 128.3 (2), 128.6 (2), 128.7 (2) and 129.0 (2) (10 × ArCH), 140.2 and 140.4 (2 × ArC). MS (EI), *m*/*z* (%): 212.1 $(M + H)^+$ (100), and 253.2 $(M + 42)^+$ (15).

***N*-Benzylnaphthalen-1-ylmethylamine (4g) [14393-12-5].** Yield: 72%. t_R/min: 11.8. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.82 (br, 1H, NH), 3.98 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.35–7.57 (m, 9H, ArH), 7.85 (d, J = 8.1 Hz, 1H, ArH), 7.93 (d, J = 8.1 Hz, 1H, ArH), and 8.16 (d, J = 8.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 51.0 (CH_2), 53.9 (CH_2), 124.0, 125.6, 125.8, 126.3, 126.4, 127.3, 128.0, 128.5 (2), 128.7 (2) and 128.9 (12 × ArCH), 132.1, 134.1, 135.9 and 140.4 (4 × ArC). MS (EI), *m*/*z* (%): 248.2 $(M + H)^+$ (100), 249.3 $(M + 2)^+$ (18), and 298.2 $(M + 52)^+$ (31).

***N*-(Furan-2-ylmethyl)-1-methylbutylamine (4h).** Yield: 69%. t_R/min: 8.7. ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.91 (t,

‡ CAS registry numbers are given for known compounds.

J = 7.5 Hz, 3H, Me), 1.06 (d, J = 6.0 Hz, 3H, Me), 1.29–1.49 (m, 4H, 2 × CH_2), 1.72 (br, 1H, NH), 2.63–2.71 (m, 1H, N-CH), 3.75 (d, J = 14.7 Hz, 1H, CH), 3.83 (d, J = 14.1 Hz, 1H, CH), 6.17 (d, J = 3.0 Hz, 1H, ArH), 6.31 (dd, J = 3.0 and 2.1 Hz, 1H, ArH), and 7.36 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.4 (Me), 19.3 (CH_2), 20.2 (Me), 39.3 (CH_2), 43.8 (CH_2), 51.9 (CH), 106.8, 110.2 and 141.8 (3 × ArCH), and 154.3 (ArC).

***N*-Benzyl-1-methylbutylamine (4i) [61806-76-6].** Yield: 83%. t_R/min: 9.8.^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.93 (t, J = 7.5 Hz, 3H, Me), 1.10 (d, J = 6.6 Hz, 3H, Me), 1.30–1.55 (m, 4H, 2 × CH_2), 2.66–2.76 (m, 1H, N-CH), 3.75 (d, J = 12.5 Hz, 1H, CH), 3.85 (d, J = 12.5 Hz, 1H, CH), 7.33 (s, 3H, ArH), and 7.35 (s, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.5 (Me), 19.4 (CH_2), 20.5 (Me), 39.5 (CH_2), 51.5 (CH_2), 52.4 (CH), 127.0, 128.3 (2) and 128.5 (2) (5 × ArCH), and 141.0 (ArC). MS (EI), m/z (%): 178.0 $(M + H)^+$ (100).

***N*-(1-Methylbutyl)pyridin-2-ylmethylamine (4j).** Yield: 87%. t_R/min: 8.2. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.86 (t, J = 7.5 Hz, 3H, Me), 1.05 (d, J = 6.6 Hz, 3H, Me), 1.24–1.50 (m, 4H, 2 × CH_2), 2.27 (br, 1H, NH), 2.61–2.67 (m, 1H, N-CH), 3.81 (d, J = 13.2 Hz, 1H, CH), 3.90 (d, J = 14.0 Hz, 1H, CH), 7.10 (dd, J = 7.4 and 5.2 Hz, 1H, ArH), 7.25 (d, J = 7.5 Hz, 1H, ArH), 7.57 (td, J = 7.5 and 1.5 Hz, 1H, ArH), and 8.49 (d, J = 5.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.4 (Me), 19.3 (CH_2), 20.3 (Me), 39.5 (CH_2), 52.7 (CH_2), 52.8 (CH), 122.0, 122.5, 136.5 and 149.3 (4 × ArCH), and 160.1 (ArC). MS (EI), m/z (%): 179.1 $(M + H)^+$ (100).

***N*-Benzhydryl-1-methylbutylamine (4k).** Yield: 68%. t_R/min: 12.3. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.98 (t, J = 7.4 Hz, 3H, Me), 1.16 (d, J = 6.0 Hz, 3H, Me), 1.38–1.61 (m, 4H, 2 × CH_2), 1.81 (br, 1H, NH), 2.66–2.72 (m, 1H, N-CH), 5.28 (s, 1H, N-CH-Ph_2), and 7.28–7.52 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.6 (Me), 19.4 (CH_2), 20.8 (Me), 40.1 (CH_2), 50.2 (CH), 64.3 (N-CH), 127.2 (4), 127.7 (2), and 128.7 (4) (10 × ArCH), and 145.8 (2 × ArC). MS (EI), m/z (%): 254.2 $(M + H)^+$ (100).

***N*-(2,2-Diphenylethyl)-1-methylbutylamine (4l).** Yield: 69%. t_R/min: 12.7. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.88 (t, J = 7.4 Hz, 3H, Me), 1.06 (d, J = 6.6 Hz, 3H, Me), 1.18–1.47 (m, 4H, 2 × CH_2), 2.63–2.73 (m, 1H, N–CH), 3.22 (dd, J = 11.0 and 8.1 Hz, 1H, CH), 3.32 (dd, J = 11.0 and 8.1 Hz, 1H, CH), 4.23 (t, J = 8.1 Hz, 1H, CH), and 7.21–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.4 (Me), 19.3 (CH_2), 20.5 (Me), 39.4 (CH_2), 51.5 (CH), 52.2 (CH_2), 53.1 (CH), 126.7 (2), 128.2 (4), and 128.8 (4) (10 × ArCH), and 143.2 (2 × ArC). MS (EI), m/z (%): 268.3 $(M + H)^+$ (100).

***N*-(1-Methylbutyl)phenethylamine (4m) [71797-48-3].** Yield: 85%. t_R/min: 10.4. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.91 (t, J = 7.5 Hz, 3H, Me), 1.05 (d, J = 6.6 Hz, 3H, Me), 1.22–1.47 (m, 4H, 2 × CH_2), 2.59–2.69 (m, 1H, N-CH), 2.73–3.00 (m, 4H, 2 × CH_2), 7.23 (d, J = 6.6 Hz, 3H, ArH), and 7.29 (d, J = 6.9 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.4 (Me), 19.3 (CH_2), 20.4 (Me), 36.7 (CH_2), 39.5 (CH_2), 48.8 (CH_2), 53.0 (CH), 126.3, 128.6 (2) and 128.8 (2) (5 × ArCH), and 140.3 (ArC). MS (EI), m/z (%): 192.1 $(M + H)^+$ (100).

***N*-(1-Methylbutyl)naphthalen-1-ylmethylamine (4n).** Yield: 71%. t_R/min: 11.6. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.96 (t, J = 7.4 Hz, 3H, Me), 1.21 (d, J = 6.6 Hz, 3H, Me), 1.34–1.65 (m, 4H, 2 × CH_2), 2.80–2.90 (m, 1H, N-CH), 4.21 (d, J = 13.2 Hz, 1H, CH), 4.31 (d, J = 13.2 Hz, 1H, CH), 7.43–7.60 (m, 4H, ArH), 7.80 (d, J = 8.1 Hz, 1H, Ar), 7.90 (d, J = 8.1 Hz, 1H, Ar), and 8.16 (d, J = 8.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 14.5 (Me), 19.5 (CH_2), 20.7 (Me), 39.6 (CH_2), 49.5 (CH_2), 53.4 (CH), 123.9, 125.6, 125.8, 126.3 (2), 127.9 and 128.9 (7 × ArCH), 132.0, 134.1, and 136.6 (3 × ArC). MS (EI), m/z (%): 228.1 $(M + H)^+$ (100).

***N*,*N*′-Dibenzylcyclohexane-1,4-diamine (5a).** Yield: 38%. t_R/min: 8.4. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.14–1.20 (m, 8H, 4 × CH_2), 1.94–2.00 (m, 2H, 2 × NH), 2.44–2.56 (m, 2H, N-CH), 3.80 (s, 4H, 2 × CH_2), 7.31 (s, 6H, ArH), and 7.32 (s, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 32.2 (CH_2), 51.5 (N-CH), 56.4 (N-CH_2), 127.0 (2), 128.2 (4), and 128.6 (4) (10 × ArCH), and 140.9 (2 × ArC). MS (EI), m/z (%): 295.3 $(M + H)^+$ (50), and 188.0 (100).

Benzyl[4-(benzylaminomethyl)benzyl]amine (5b) [25790-41-4]. Yield: 41%. t_R/min: 9.1. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.79 (br, 2H, 2 × NH), 3.845 (s, 4H, 2 × CH_2), 3.853 (s, 4H, 2 × CH_2), and 7.36–7.40 (m, 14H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm): 53.1 (CH_2), 53.3 (CH_2), 127.2 (2), 128.37 (4), 128.44 (4) and 128.6 (4) (14 × ArCH), 139.2, and 140.5 (2) (3 × ArC). MS (EI), m/z (%): 317.3 $(M + H)^+$ (100), and 200.2 (77).

Reaction of ketoester resin with benzylamine

A suspension of benzylamine (1.0 mmol) and ketoester resin (3.0 mmol g^{-1} resin) (0.2 g, 0.6 mmol) in propan-2-ol (4.0 ml) was shaken for 48 hours at room temperature. The resin was collected and washed with propan-2-ol and THF several times. After drying *in vacuo*, the resin was analyzed by IR and gel-phase NMR in C_6D_6.

IR (ν_{max}/cm^{-1}): 697, 732, 781, 1028, 1071, 1108, 1160, 1231, 1269, 1451, 1494, 1599, 1650, 1723, 2938, and 3292. ^{13}C NMR (C_6D_6, 100 MHz, δ, ppm): 19.5 (Me), 46.9 (CH_2), 50.0 (OMe), 84.0 (=CH), 162.7 (=C–N), and 170.7 (OC=O).

Ketoester resin: IR (ν_{max}/cm^{-1}): 701, 761, 1019, 1143, 1314, 1360, 1451, 1493, 1715, and 2935. ^{13}C NMR (C_6D_6, 100 MHz, δ, ppm): 30.3 (Me), 50.2 (CH_2), 90.2 (=CH), 167.5 (OC=O), and 200.2 (C=O).

Preparation of methyl 3-benzylaminobut-2-enoate

A mixture of benzylamine (1.0 mmol) and an equimolar amount of methyl acetoacetate in methanol (20 ml) was shaken for 30 minutes at room temperature. After removal of the solvent, the residue was washed with a little hexane (2 ml) to give methyl 3-benzylaminobut-2-enoate, which was used without further purification.

Yield: 95%. IR (ν_{max}/cm^{-1}): 692, 728, 782, 846, 928, 972, 1013, 1057, 1070, 1115, 1167, 1184, 1233, 1281, 1313, 1375, 1441, 1470, 1504, 1568, 1596, 1640, 2981, and 3320. ^{1}H NMR (C_6D_6, 300 MHz, δ, ppm): 1.38 (s, 3H, Me), 3.54 (s, 3H, OMe), 3.72 (d, J = 6.0 Hz, 2H, -CH_2), 4.76 (s, 1H, =CH), 7.01 (m, 5H, ArH), and 9.31 (br, 1H, NH). ^{13}C NMR (C_6D_6, 75 MHz, δ, ppm): 19.0 (Me), 46.5 (CH_2), 50.0 (OMe), 83.9 (=CH), 126.8 (2), 127.4, and 129.0 (2) (5 × ArCH), 139.7 (ArC), 161.8 (=C–N), and 171.3 (MeOC=O). MS (EI), m/z (%): 206.1 $(M + H)^+$ (100), and 207.1 $(M + 2)^+$ (15).

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