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Reagent concentration effects in the REM resin solid phase synthesis of tertiary amines

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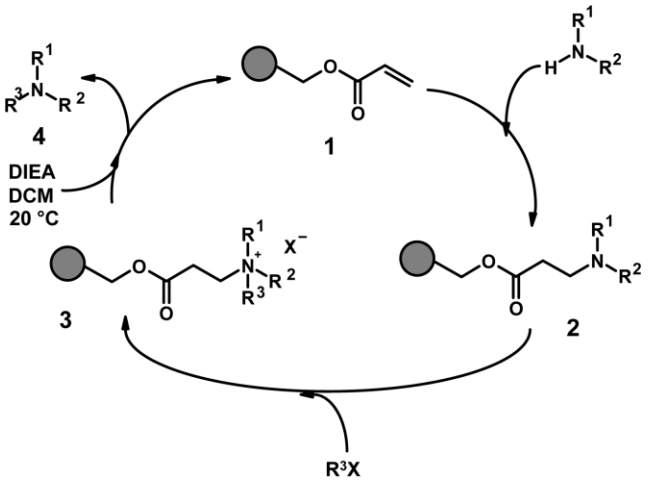
Abstract—The use of reagent concentration has resulted in increased rates for all stages of the REM resin synthesis of tertiary amines. These increases in rate translate into faster reaction times, higher yields and lower reagent consumption. Of the methods examined, the most successful was the use of perfluorous solvents, either alone or with a small amount of organic co-solvent.

1. Introduction

The use of solid phase organic synthesis as a tool for the synthesis of chemical libraries is an area of great importance in both academia and in the pharmaceutical industry.[1] One of the drawbacks to such methodology, however, is the large excesses of reagents and extended reaction times often required to force solid phase reactions to completion. The use of excess reagents is particularly undesirable from an environmental point of view and from an economic standpoint in the case of costly or commercially unavailable reagents. One possible strategy to combat these drawbacks is the use of reagent concentration effects, whereby the effective concentration of reagent at the functionalised sites of the resin is increased. The simplest way to concentrate reagents is of course to lower solvent volumes,[2] or remove solvent from the process altogether. Another possible approach is the use of solvents in which the reagents are poorly soluble, resulting in an increased concentration of reagents within the polymer.[3] A particularly successful group of solvents here are the perfluorous organic solvents which are well known for their immiscibility with common organic solvents,[4] and have recently been shown to provide reagent concentration in the REM resin cycle.[5] Herein we present our results using reagent concentration in the synthesis of 3° amines on REM resin.

REM resin methodology is an efficient approach for the solid phase synthesis of 3° amines.[6] In its simplest form the REM resin, **1** undergoes Michael addition with a 2° amine to give a polymer bound 3° amine, **2**. Quaternisation of **2** with an alkyl halide then gives a quaternary ammonium salt **3**, which on exposure to a mild base releases the 3° amine product **4** from the resin (Hofmann elimination) whilst regenerating starting material **1** (Scheme 1).



Scheme 1.

2. Results and discussion

2.1. Michael addition

Our initial efforts into the application of reagent concentration effects in the REM resin cycle were concentrated on the Michael addition (**1**→**2**) where, under standard conditions, 5–10 equiv. of amine and 18 h reaction times in *N*,*N*-dimethylformamide (DMF) are required. In order to investigate the possibility of reagent concentration within this process REM resin **1** (polystyrene with 1% divinylbenzene crosslinking, 2 mmol/g) was suspended in various

Keywords: tertiary amines; perfluorous solvents; polymer support; reagent concentration; solid-phase synthesis; REM resin.

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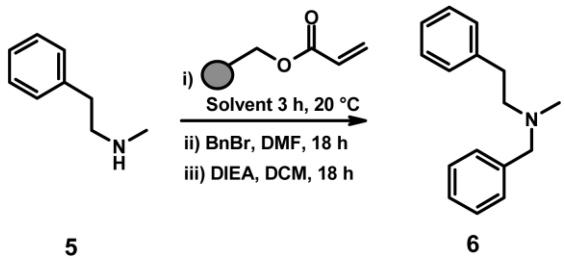


Scheme 2.

solvents in the presence of amine **5** (2 equiv.) at 20°C for 3 h (Scheme 2).[5a] This was followed by standard quaternisation (BnBr 10 equiv., DMF, 18 h) and cleavage (DIEA 2 equiv., DCM, 6 h) to give the expected product **6**. The yields are shown in Table 1. Product purities were effectively independent of solvent and were greater than 90% as determined by HPLC.

As anticipated aliphatic perfluorous solvents gave significantly greater yields than DMF, which failed to give any product under standard dilution conditions (Table 1, entry 1 versus entries 14–17). Interestingly, aromatic perfluorous solvents did not give any product. When perfluorohexane was combined with a small amount of either DMSO or DMF as a co-solvent the yield was generally greater than three times that observed when that volume of co-solvent was used alone (Table 1, entries 18, 19 versus entries 2, 4), although the yield seen with only a small volume of co-solvent was itself significantly greater than that seen when the standard volume of solvent was used. The yield seen when perfluorohexane was used in conjunction with a co-solvent was similar to that seen when neat amine (150 equiv.) was used as solvent. The success when a small amount of co-solvent was used in conjunction with a perfluorous solvent was thought to be due to a solvation effect within the resin. Presumably the perfluorous species cannot enter the resin and so the only liquid within the resin interior will be the amine reagent. By using a small amount of co-solvent the liquid volume can be increased to a level more conducive to diffusion throughout all the resin beads and allow some resin swelling. The high yields seen with perfluorous solvents were particularly surprising when it is considered that the resins used showed little or no swelling in these solvents (swelling of 1 in DMF=4.4 mL/g, in perfluorohexane=0.4 mL/g, in perfluorohexane with 1 μL DMF per mg resin=1.7 mL/g).[7] The use of other solvents in which amine solubility and resin swelling were poor gave mixed results with water and methylcyclohexane giving no product and approximately 40% **6** seen when silane based solvents were used in conjunction with a co-solvent (Table 1, entries 6, 7, 9, 11). In order to confirm that the elevated yields seen with perfluorohexane were due to a reagent concentration effect, the effect on the yield of **6** of varying the amount of perfluorohexane was investigated (Table 2). The results seemed to confirm the reagent concentration hypothesis with quantitative yields of product at all volumes

Table 1.

Entry	Solvent	Yield[a] (%) **6**
1	DMF	<5
2	DMF—0.03 mL	29
3	DMSO	<5
4	DMSO—0.03 mL	24
5	Neat amine[b]	>95
6	Water	<5
7	Methylcyclohexane	<5
8	Hexamethyldisiloxane	<5
9	Hexamethyldisiloxane and 0.03 mL DMF[c]	38
10	Silicone 200	8
11	Silicone 200 and 0.03 mL DMF[c]	43
12	Hexafluorobenzene	<5
13	Octafluorotoluene	<5
14	Perfluorodecalin	58
15	Perfluorotripropylamine	65
16	Perfluoromethylcyclohexane	46
17	Perfluorohexane	57
18	Perfluorohexane and 0.03 mL DMSO[c]	88
19	Perfluorohexane and 0.03 mL DMF[c]	94
20	None	<5

Michael reaction performed with 0.05 mmol resin and 0.1 mmol amine at 20°C for 3 h. Solvent volume was 1 mL unless otherwise stated.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.
[b] Approx. 150 equiv. amine used as solvent.
[c] Represents the use of a standard amount (1 mL) of the named solvent with 0.03 mL DMSO/DMF.

Table 2.

Entry	Perfluorohexane (mL) and DMF (0.03 mL)	Yield[a] (%) **6**
1	0	13
2	0.05	15
3	0.1	17
4	0.15	16
5	0.2	50
6	0.25	>95
7	0.5	>95
8	0.75	>95
9	1	>95
10	2	>95
11	5	>95

Michael reaction performed with 0.05 mmol resin and 0.1 mmol amine at 20°C for 3 h. The amount of perfluorohexane was varied as indicated.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.

Table 3.

	Yield (%)[a]		
Entry	Volume of DMF added (mL)	DMF only[b]	Perfluorohexane and DMF[c]
1	0.01	18	76
2	0.03	12	75
3	0.04	<5	74
4	0.05	<5	76
5	0.075	<5	65
6	0.1	<5	64
7	0.125	<5	64
8	0.15	<5	60
9	0.175	<5	60
10	0.2	<5	59
11	0.3	<5	30
12	0.4	<5	18
13	0.5	<5	<5

Michael reaction (0.05 mmol resin, 0.1 mmol amine) performed for 2 h.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.
[b] Michael reaction performed in DMF.
[c] Michael reaction performed in perfluorohexane (1 mL) with the stated amount of DMF added.

Table 4.

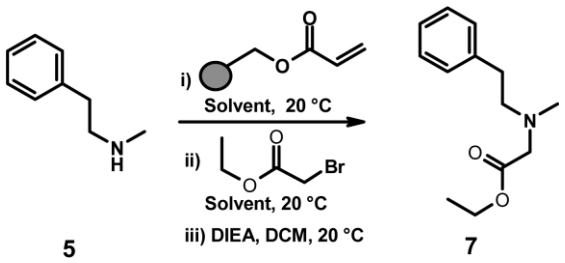
Equiv. amine **5**	Yield (%)[a]						
	No Solvent[b]	DMF[c]	DMF 0.03 mL	DMSO 0.03 mL	Perfluorohexane[c]	Perfluorohexane and DMF[d] 0.03 mL	Perfluorohexane and DMSO[d] 0.03 mL
2	26	<5	12	41	62	75	80
4	44	8	13	43	>95	83	94
6	48	14	23	50	>95	91	90
8	63	30	40	70	>95	95	94
10	65	28	56	74	>95	90	95
15	72	39	73	>95	>95	>95	>95
20	>95	73	92	>95	>95	>95	95

Michael reaction performed for 2 h.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.
[b] Amine was pipetted onto dry resin.
[c] All reactions performed with 0.05 mmol resin in 1 mL solvent unless otherwise stated.
[d] Represents the use of a standard amount (1 mL per 0.05 mmol resin) of perfluorohexane with 0.03 mL DMSO/DMF.

Table 5.

Entry	Solvent	Yield[a] (%) **6**
1	DMF	<5
2	DMF—0.2 mL	6
3	DMF—0.1 mL	9
4	DMF—0.05 mL	13
5	Perfluorohexane	20
6	Perfluorohexane and 0.2 mL DMF[b]	55
7	Perfluorohexane and 0.1 mL DMF[b]	64
8	Perfluorohexane and 0.05 mL DMF[b]	44
9	None	5

Michael reaction performed with 0.05 mmol PS-PEG resin and 0.1 mmol amine at 20°C for 3 h. Solvent volume was 1 mL unless otherwise stated.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.
[b] Represents the use of a standard amount (1 mL) of the perfluorohexane with the stated amount DMF.



Scheme 3.

of perfluorohexane greater than that required to completely cover the resin (Table 2, entries 1–5 versus 6–11).

Next, it was decided to investigate the effect of the volume of co-solvent on reaction efficiency in the synthesis of **6** (Table 3). As can be seen, when DMF was used alone some degree of reagent concentration could be seen at solvent volumes up to 0.03 mL (Table 3, entries 1 and 2). With perfluorohexane and a co-solvent, however, approximately 75% yield was seen for all solvent volumes up to 0.05 mL (Table 3, entries 1–4). The yield then began to decrease as the reagent solution was diluted, although increases in yield compared to the same volume of DMF alone were seen with up to 0.4 mL of DMF (Table 3, entries 5–12). This may have implications for other reactions where appreciable volumes of co-solvent are required to solubilise reagents.

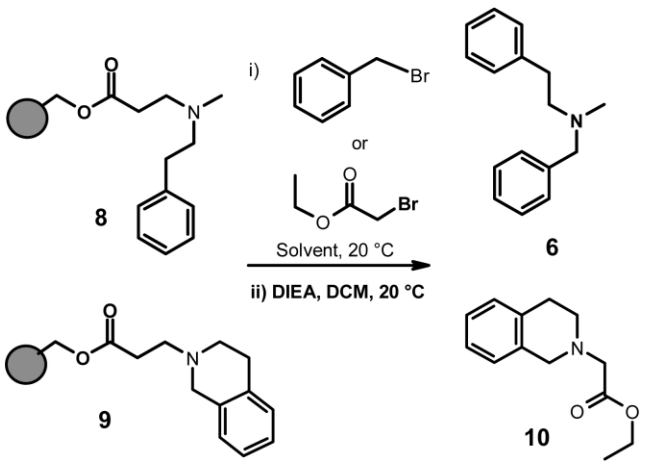
The effect of amount of amine on the yield of **6** was also investigated (Table 4). Here amine **5** was added in varying amounts to REM resin and agitated at 20°C for 2 h before standard quaternisation and cleavage with benzyl bromide. Under standard conditions (DMF, 1 mL) the reaction could not be forced to greater than 73% completion even when 20 equiv. of **5** were used. This situation could be improved by using a small amount of DMF or DMSO as solvent, or by performing the reaction under solvent-free conditions. In agreement with previous observations the best results were seen when perfluorohexane was used either alone or in conjunction with a small amount of co-solvent.

A reagent concentration effect was also observed with poly(ethylene glycol), (PS-PEG) based graft co-polymers (Table 5). Here a PS-PEG REM resin was prepared (0.48 mmol/g) and suspended in various solvents in the presence of amine **5** (2 equiv.) at 20°C for either 3 or 6 h (Scheme 2). This was followed by standard quaternisation and cleavage as outlined previously in the text. Whilst yields were generally lower than those observed with polystyrene based resins the same trend was observed with

Table 6.

Conditions	Total time (h)	Yield[a] (%) **7**
Michael—10 equiv. **5**, DMF, 18 h, quaternisation—5 equiv., DMF, 18 h, elimination—2 equiv. DIEA, DCM, 6 h	42	68
Michael—5 equiv. **5**, perfluorohexane and DMSO (0.03 mL), 2 h, quaternisation—20 equiv., DMSO, 1 h, elimination—4 equiv. DIEA, DCM, 1 h	4	>95
Michael—5 equiv. **5**, DMF, 2 h, quaternisation—20 equiv., DMSO, 1 h, elimination—4 equiv. DIEA, DCM, 1 h	4	7

Reaction performed on 0.05 mmol. Solvent volume was 1 mL unless otherwise stated.
[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.



Scheme 4.

the highest amount of product being seen when perfluorohexane was used in conjunction with a small amount of co-solvent. The fact that the optimal amount of co-solvent was higher in this case is, in all likelihood, simply a consequence of the larger amounts of the lower loading PS-PEG resin required.

In order to demonstrate the utility of the reagent concentration effect using perfluorous solvents the REM resin synthesis of **7** from amine **5** and ethyl bromoacetate was undertaken (Scheme 3, Table 6).

As can be seen, when the synthesis of **7** is attempted under standard conditions it takes a total time of 42 h and 68% of the theoretical yield is obtained. By using perfluorous solvent in the Michael reaction and an excess of ethyl bromoacetate in DMSO for the quaternisation the time taken for the synthesis can be reduced to 4 h and the yield is quantitative. Using the same regime with DMF as the solvent for the Michael reaction solvent results in a poor 7% yield.

Table 7.

Entry	Solvent	Yield[a] (%) **6**	Yield[a] (%) **10**
1	DMF	75	29
2	DMSO	43	46
3	DMSO—0.03 mL	31	53
4	Neat quaternisation reagent[b]	88	12
5	Water	49	NA[c]
6	Perfluoromethylcyclohexane	NA[c]	63
7	Perfluorotripropylamine	NA[c]	62
8	Perfluorohexane	92	63
9	Perfluorohexane and 0.03 mL DMSO[d]	>95	>95
10	None	13	47

Quaternisation reaction performed with 0.05 mmol resin and 0.1 mmol quaternisation reagent (**6**) or 0.25 mmol quaternisation reagent (**10**) at 20°C for 3 h. Solvent volume was 1 mL unless otherwise stated.

[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.

[b] Approx. 150 equiv. quaternisation reagent used as solvent.

[c] Reaction not attempted.

[d] Represents the use of a standard amount (1 mL) of the named solvent with 0.03 mL DMSO.

2.2. Quaternisation

The quaternisation reaction (Scheme 1, **2→3**) has previously been identified as both the slowest and yield limiting segment of the standard REM resin process,[6b] and so this reaction seemed to offer an ideal opportunity for reagent concentration. We have previously reported a reagent concentration effect when using DMSO as the solvent for quaternisation and subsequent increases in yield over the standard DMF.[6c] In order to investigate the quaternisation process REM resin bound *N*-methylphenethylamine (polystyrene with 1% divinylbenzene crosslinking, 1.3 mmol/g), **8** and tetrahydro isoquinoline (polystyrene with 1% divinylbenzene crosslinking, 1.2 mmol/g), **9** were prepared and quaternised in various solvents with either benzyl bromide or ethyl bromoacetate to give, after standard cleavage **6** or **10**, respectively (Scheme 4). The results are shown in Table 7.

As can be seen increases in yield were also seen in the quaternisation reaction on switching from the standard solvents to perfluorous solvents and the best results were observed when perfluorohexane was used in conjunction with a small amount of DMSO as co-solvent. The thorough washing of the resin to remove all traces of perfluorous solvents and the excess quaternisation reagent trapped within the resin was of paramount importance here as any residual quaternisation reagent could go on to quaternisation the product as it was cleaved from the resin in the next stage. The use of a small amount of DMSO alone generally gave similar yields to the normal amount of solvent (Table 7, entry 2 versus 3). Interestingly, some product was also seen when water was employed as solvent (Table 7, entry 5), presumably also a result of the concentration of reagents within the resin.

One possible concern with the use of perfluorous solvents in solid phase chemistry is an adverse effect on reaction kinetics due to the lack of swelling with lightly cross-linked resins. Macroporous resins, however, are designed to give minimal swelling and so would seem ideally suited to applications involving perfluorous solvents. With this in mind, macroporous REM resins corresponding to **8** (polystyrene with 20% divinylbenzene crosslinking, 0.79 mmol/g) and **9** (polystyrene with 20% divinylbenzene crosslinking, 0.74 mmol/g) were prepared by reaction with the corresponding amine. These were then quaternised as in Scheme 4 to give, after standard cleavage, tertiary amines **6** or **10** (Table 8).

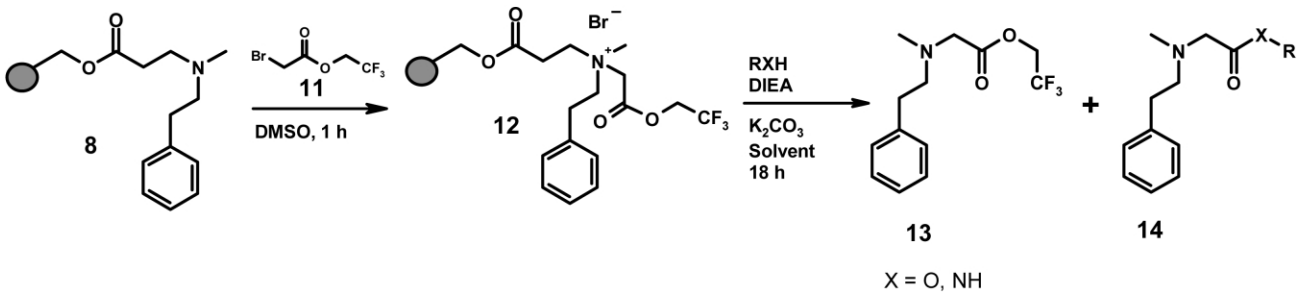
Table 8.

Entry	Solvent	Yield[a] (%) **6**	Yield[a] (%) **10**
1	DMF	44	17
2	Perfluoromethylcyclohexane	65	56
3	Neat quaternisation reagent[b]	31	14

Quaternisation reaction performed with 0.05 mmol macroporous resin and 0.1 mmol quaternisation reagent (**6**) or 0.25 mmol quaternisation reagent (**10**) at 20°C for 3 h. Solvent volume was 1 mL.

[a] Yields determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard.

[b] Approx. 150 equiv. quaternisation reagent used as solvent.



Scheme 5.

As anticipated, the use of perfluorous solvents resulted in considerable increases in yield compared to the standard solvents. However, as the yields seen here were considerably lower than those seen for the corresponding microporous resins no further studies with macroporous matrices were undertaken.

2.3. Hofmann elimination/transesterification

At first sight the Hofmann elimination reaction (Scheme 1, **3→4**) offers few opportunities for reagent concentration, being a facile process which can be performed quantitatively in 1 h (Table 6). By incorporating a transesterification reaction into the Hofmann elimination step, however, an opportunity for reagent concentration was discovered.[5b] The use of 2,2,2-trifluoroethanol esters as activating groups in peptide coupling and transesterification reactions has been previously reported.[8] It was thought that by incorporating such a moiety into the alkyl halide quaternisation reagent, a REM resin bound activated ester would be obtained that could be cleaved from the resin and transesterified in one-pot. In this way a large batch of polymer bound quaternary ammonium salt **3** could be prepared and then split into numerous smaller batches for the synthesis of an array of esters and amides by transesterification with alcohols and amines, respectively. It was hoped that reagent concentration would favourably affect the transesterification equilibrium. In order to test this hypothesis, REM resin bound *N*-methylphenethyl amine **8** (polystyrene with 1% divinylbenzene crosslinking, 1.23 mmol/g), was quaternised with halide **11** (20 equiv., DMSO, 20°C, 1 h) and subjected to Hofmann elimination conditions in the presence of varying amounts of methanol (Scheme 5, X=O, R=CH_3).[5] The results are shown in Table 9.

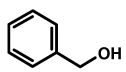
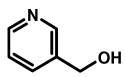
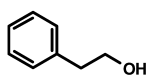
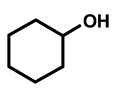
For reaction in DCM, although transesterification did occur, the process did not proceed to completion with less than

Table 9.

Entry	Solvent[a]	Equiv. MeOH	Conversion (%)[b]
1	DCM	2	18
2	DCM	5	49
3	DCM	10	76
4	DCM	20	86
5	DCM	30	>95
6	DCM (0.1 mL)	5	70
7	DCM (0.05 mL)	5	58
8	Perfluorohexane	2	>95
9	Perfluorohexane	5	>95
10	Perfluorohexane and DCM (0.1 mL)	5	65
11	Perfluorohexane and DCM (0.05 mL)	5	90
12	None	5	55

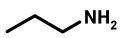
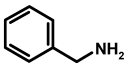
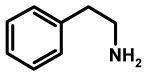
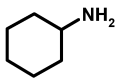
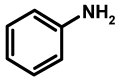
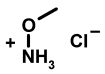
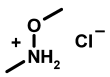
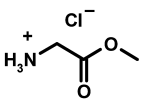
Quaternisation (0.05 mmol resin, 1 mmol **11**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIEA 2 equiv., K_2CO_3 4 equiv., MeOH, solvent 1 mL).
[a] Solvent was 1 mL unless otherwise stated.
[b] Conversion determined by ^{1}H NMR ($CDCl_3$).

Table 10.

Entry	Alcohol	Equiv.	Solvent	Conversion (%)[a]
1	MeOH	5	DCM	49
			Perfluorohexane	>95
			None	55
2	EtOH	10	DCM	25
			Perfluorohexane	>95
			None	65
3		5	DCM	28
			Perfluorohexane	>95
			None	69
4		2.5	DCM	59
			Perfluorohexane	>95
			None	70
5		2.5	DCM	39
			Perfluorohexane	>95
			None	41
6		10	DCM	28
			Perfluorohexane	>95
			None	57
7		20	DCM	<5
			Perfluorohexane	64
			None	<5
8		10	DCM	<5
			Perfluorohexane	50
9		20	DCM	<5
			Perfluorohexane	<5

Quaternisation (0.05 mmol resin, 1 mmol **11**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIEA 2 equiv., K_2CO_3 4 equiv., ROH, solvent). Solvent volume was 1 mL.
[a] Conversion determined by ^{1}H NMR ($CDCl_3$).

Table 11.

Entry	Amine	Equiv.	Solvent	Conversion (%)[a]
1		5	DCM	88
			Perfluorohexane	>95
			None	>95
2		5	DCM	78
			Perfluorohexane	>95
			None	>95
3		5	DCM	88
			Perfluorohexane	>95
			None	>95
4		5	DCM	>95
			Perfluorohexane	>95
			None	>95
5		5	DCM	20
			Perfluorohexane	83
			None	83
6		20	DCM	<5
			Perfluorohexane	<5
			None	<5
7		20	DCM	<5
			Perfluorohexane	<5
			None	<5
8		5	DCM	50
			Perfluorohexane and DCM (0.1 mL)	88
9		5	DCM	<5
			Perfluorohexane and DCM (0.1 mL)	<5
10		5	DCM	17
			Perfluorohexane and DCM (0.1 mL)	81

Quaternisation (0.05 mmol resin, 1 mmol **11**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIEA 2 equiv., K_2CO_3 4 equiv., RNH_2, solvent). Solvent volume was 1 mL.

[a] Conversion determined by ^1H NMR ($CDCl_3$).

30 equiv. of methanol (Table 9, entries 1–5). Clearly, although this was not a problem in the case of methanol, where the alcohol is readily available in large quantities and any excess could be removed by evaporation, it could become a problem when using commercially unavailable or non-volatile reagents. The extent of transesterification could be improved, however, with the use of low solvent volumes (Table 9, entry 6), solvent-free conditions (Table 9, entry 12) or perfluorous solvents (Table 9, entries 8→11). The best results were seen when perfluorohexane was used as solvent, with essentially complete transesterification when 2 or more equivalents of ethanol were applied. Interestingly, the use of perfluorohexane with a small volume of DCM as co-solvent tended to depress reaction in this case. It was unclear at which point during the process the transesterification reaction occurred. Presumably resin bound intermediate **12** would be more reactive towards transesterification due to the influence of the quaternary nitrogen. However, trifluoroester **13** was found to undergo complete transesterification in solution when exposed to identical conditions to those used in Table 1, entry 5. No transesterification was observed under any conditions when the 2,2,2-trifluoroethanol ester was replaced with simple alkyl esters. At first sight, the success of transesterification in perfluorohexane was thought to be a result of the miscibility of the liberated trifluoroethanol with the

perfluorous solvent. This would effectively remove any trifluoroethanol from the reaction and so help drive the equilibrium towards complete transesterification. However, this was shown not to be the case since the two species are in fact immiscible.

Having established the feasibility of the one-pot Hofmann elimination/transesterification protocol the reaction was performed on a number of different alcohols (Table 10). None of the alcohols used gave complete conversion under standard conditions, although in most cases an improvement was seen when the reaction was performed under solvent-free conditions. All of the 1° alcohols used gave complete conversion to the desired ester when perfluorohexane was used as the solvent (Table 10, entries 1→6). With standard solvents no product could be detected when 2° alcohols were used as the nucleophilic species although this was increased to approximately 50% by the use of perfluorohexane (Table 10, entries 7→8). No transesterification was seen under any conditions with a 3° alcohol (Table 10, entry 9).

The use of 1° amines to give, after Hofmann elimination, α-amino acid amides (Scheme 5, X=NH) was also successful (Table 11). The conversions seen were generally much higher than for the corresponding alcohols, with complete conversion seen for many amines under either solvent-free or perfluorous conditions. Hydroxylamines and α-amino acids were also suitable nucleophiles for the transesterification process (Table 11, entries 8 and 10). Aniline gave no transesterification products (Table 11, entry 6) and the use of 2° amines to give 3° amides was equally unsuccessful (Table 11, entries 7 and 9).

When volatile nucleophiles were used in the process, any excess was simply removed by evaporation. Excesses of nucleophile for which this treatment was not amenable were removed by the use of a polymer-supported sulphonyl chloride (for alcohols),[9] or isocyanate (for amines)[10] scavenger reagent.

3. Conclusions

In conclusion, we have shown that the use of reagent concentration methods in the REM resin synthesis of 3° amines resulted in increased rates in comparison with the standard solvent systems which can be translated into higher yields, shorter reaction times and a reduction in the excesses of reagents required. The methods that showed the best results were the use of low solvent volume or solvent-free conditions or more generally the use of perfluorous solvents, either with or without a small amount of organic co-solvent.

4. Experimental

4.1. General

All resins were purchased from Argonaut Technologies. REM resin synthesis was performed according to published procedures.[6b] Loading levels of REM resin were determined by complete Michael reaction (by I.R.) and elemental analysis (N determination was performed on a Perkin–Elmer 2400 elemental analyser). Solvents and commercially available reagents were used as received with no further purification. Nuclear magnetic resonance were recorded at 400 MHz using a Bruker DPX instrument, where appropriate yield was determined by ^{1}H NMR using *N*-methylmaleimide as an internal standard ($CDCl_3$ solution, 0.05 mmol/mL). Mass spectra were recorded on a API150EX LC-MS instrument, High resolution mass spectra were recorded on a Mariner TOF instrument with perfluorokerosene as an internal standard. Infrared spectra of products were recorded on a Perkin–Elmer Spectrum 1000 FT-IR instrument as thin films.

4.2. General procedure for Michael addition *N*-benzyl-*N*-methylphenethylamine 6

REM resin (0.05 mmol) was treated with *N*-methylphenethylamine (0.1–1 mmol) and the appropriate solvent. The mixture was then agitated at 20°C for 2–3 h, filtered and the resin washed (3×1 mL, DMF, DCM, MeOH). The precipitate was then air-dried, resuspended in DMF (1 mL) and treated with benzyl bromide (0.5 mmol). The suspension was agitated at 20°C for 18 h, filtered, washed (3×1 mL DMF, DCM, MeOH) and resuspended in DCM (1 mL). The suspension was treated with DIEA (0.1 mmol) and K_2CO_3 (0.2 mmol) and agitated at 20°C for 6 h. The mixture was then filtered, the resin washed (3×1 mL DCM) and the organic washings concentrated in vacuo. The product *N*-benzyl-*N*-methylphenethylamine **6** was spectroscopically identical to the previously published data.[11]

4.2.1. Procedure for the REM resin synthesis of (*N*-methylphenethylamino)-acetic acid ethyl ester (7) in 4 h. REM resin (0.05 mmol, 2 mmol/g, 25 mg) was treated with *N*-methylphenethylamine (0.25 mmol), DMSO (0.03 mL) and perfluorohexane (1 mL). The mixture was then agitated at 20°C for 2 h, filtered and the resin washed (3×1 mL, DMF, DCM, MeOH). The precipitate was then air-dried, suspended in DMSO (1 mL) and treated with ethylbromoacetate (1 mmol). The suspension was agitated at 20°C for 1 h, filtered, washed (3×1 mL DMF, DCM, MeOH) and resuspended in DCM (1 mL). The suspension was treated with DIEA (0.2 mmol) and K_2CO_3 (0.2 mmol) and agitated at 20°C for 1 h. The mixture was then filtered, the resin washed (3×1 mL DCM) and the organic washing concentrated in vacuo to give the product as a colourless oil. This material has been previously reported.[12] ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**7**); 1.24 (t, 3H, J=7.1 Hz, CH_3), 2.47 (s, 3H, NCH_3), 2.74–2.83 (m, 4H, CH_2N and CH_2Ar), 3.30 (s, 2H, CH_2CO), 4.21 (q, 2H, J=7.0 Hz, OCH_2), 7.18–7.21 (m, 3H, ArH), 7.24–7.29 (m, 2H, ArH); IR (film) 1740, 1454, 1176 cm^{-1}; HRMS 222.1482 (MH^+), $C_{13}H_{20}NO_2$ requires 222.1488.

4.2.2. General procedure for quaternisation (3,4-dihydro-1*H*)-isoquinolin-2-yl)-acetic acid ethyl ester (10). REM resin bound 1,2,3,4-tetrahydroisoquinoline, **9** (0.05 mmol, 1.21 mmol/g, 41 mg) was treated with ethylbromoacetate (0.055–1 mmol) and the appropriate solvent. The mixture was then agitated at 20°C for 2–3 h, filtered and the resin washed (1×1 mL DCM, 3×1 mL 1:1 (v/v) toluene/heptane, DCM, DMF, DCM, MeOH). The

precipitate was then air-dried and resuspended in DCM (1 mL). The suspension was treated with DIEA (0.1 mmol) and K_2CO_3 (0.2 mmol) and agitated at 20°C for 6 h. The mixture was then filtered, the resin washed (3×1 mL DCM) and the organic washings concentrated in vacuo to give the product as a pale yellow oil. This material has been previously reported.[13] ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**10**); 1.27 (t, 3H, J=7.3 Hz, CH_3), 2.82–2.94 (m, 4H, CH_2N and CH_2Ar), 3.30 (s, 2H, CH_2CO), 3.80 (s, 2H, CH_2Ar), 4.22 (q, 2H, J=7.3 Hz, OCH_2), 6.98–7.03 (m, 1H, ArH), 7.08–7.13 (m, 3H, ArH).

4.2.3. 2,2,2-Trifluoroethylbromoacetate (11). Compound **11** was prepared according to a modified version of the procedure published by Hudson.[14] 2,2,2-Trifluoroethanol (230 mmol) was cooled on an acetone/ice bath with magnetic stirring and treated dropwise with bromoacetyl bromide (115 mmol). The mixture was then allowed to warm to room temperature overnight and excess 2,2,2-trifluoroethanol removed in vacuo. The residue was then washed with saturated brine (3×10 mL), diluted with diethyl ether (30 mL), dried ($MgSO_4$) and filtered through a pad of basic alumina (30 g). The alumina was flushed with diethyl ether (100 mL) and the ethereal solution concentrated in vacuo to afford **11** as a colourless liquid (20.6 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**11**); 3.92 (s, 2H, CH_2Br), 4.55 (q, 2H, J=8.0 Hz, CH_2CF$_3$).

4.2.4. General procedure for Hofmann elimination/transesterification (*N*-methylphenethylamino)-acetic acid methyl ester (14a). REM resin bound *N*-methylphenethylamine, **8** (0.05 mmol) was treated with **11** (1 mmol) and DMSO (1 mL). The mixture was then agitated at 20°C for 1 h, filtered and the resin washed (1×1 mL DCM, DMF, DCM). The precipitate was dried in vacuo and treated with methanol (0.25 mmol), K_2CO_3 (0.2 mmol), DIEA (0.1 mmol) and the appropriate solvent. The resulting suspension was agitated at 20°C for 18 h. The mixture was then filtered, the resin washed (1×1 mL DCM, 3×1 mL 1:1 (v/v) toluene/heptane, DCM) and the organic washings concentrated in vacuo to give the product as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14a**); 2.45 (s, 3H, NCH_3), 2.72–2.83 (m, 4H, CH_2N and CH_2Ar), 3.32 (s, 2H, CH_2CO), 3.79 (s, 3H, OCH_3), 7.18–7.22 (m, 3H, ArH), 7.24–7.31 (m, 2H, ArH); IR (film) 1737, 1452, 1170 cm^{-1}; m/z (ES$^+$); 208 (MH$^+$); HRMS 208.1331 (MH$^+$), $C_{12}H_{18}NO_2$ requires 208.1332.

4.2.5. (*N*-Methylphenethylamino)-acetic acid allyl ester (14b). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14b**); 2.46 (s, 3H, NCH_3), 2.77–2.84 (m, 4H, CH_2N and CH_2Ar), 3.35 (s, 2H, CH_2CO), 4.62 (d, 2H, J=5.5 Hz, OCH_2), 5.24 (dd, 1H, J=1.5, 10.5 Hz, =CH_2 –*cis*), 5.32 (dd, 1H, J=1.5, 17.1 Hz, =CH_2 –*trans*), 5.88–5.97 (m, 1H, =CH), 7.18–7.22 (m, 3H, ArH), 7.24–7.31 (m, 2H, ArH); IR (film) 1740, 1454, 1171, 1058 cm^{-1}; m/z (ES$^+$); 234 (MH$^+$); HRMS 234.1497 (MH$^+$), $C_{14}H_{20}NO_2$ requires 234.1489.

4.2.6. (*N*-Methylphenethylamino)-acetic acid benzyl ester (14c). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14c**); 2.53 (s, 3H, NCH_3), 2.77–2.86 (m, 4H, CH_2N and CH_2Ar), 3.44 (s, 2H, CH_2CO), 4.13 (t, 2H, J=6.5 Hz, OCH_2), 7.13–7.21 (m, 3H, ArH), 7.23–7.30 (m, 3H, ArH), 7.33–7.40 (m, 4H, ArH); IR (film) 1739, 1497, 1454, 1167, 1058 cm^{-1}; m/z (ES$^+$); 284 (MH$^+$); HRMS 284.1639 (MH$^+$), $C_{18}H_{22}NO_2$ requires 284.1645.

4.2.7. (*N*-Methylphenethylamino)-acetic acid pyridin-3-yl methyl ester (14d). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14d**); 2.53 (s, 3H, NCH_3), 2.79–2.91 (m, 4H, CH_2N and CH_2Ar), 3.45 (s, 2H, CH_2CO), 5.19 (s, 2H, OCH_2), 7.12–7.32 (m, 6H, ArH), 7.70 (dd, 1H, J=2.0, 8.0 Hz, ArH), 8.58 (d, 1H, J=5.0 Hz, ArH), 8.63 (s, 1H, ArH); IR (film) 1742, 1430, 1204, 1058 cm^{-1}; m/z (ES$^+$); 285 (MH$^+$); HRMS 285.1611 (MH$^+$), $C_{17}H_{21}N_2O_2$ requires 285.1598.

4.2.8. (*N*-Methylphenethylamino)-acetic acid phenethyl ester (14e). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14e**); 2.39 (s, 3H, NCH_3), 2.68–2.81 (m, 4H, CH_2N and CH_2Ar), 2.92 (t, 2H, J=6.8 Hz, CH_2Ar), 3.27 (s, 2H, CH_2CO), 4.33 (t, 2H, J=6.7 Hz, OCH_2), 7.13–7.31 (m, 10H, ArH); IR (film) 1746, 1496, 1454, 1201 cm^{-1}; m/z (ES$^+$); 298 (MH$^+$); HRMS 298.1796 (MH$^+$), $C_{19}H_{24}NO_2$ requires 298.1802.

4.2.9. (*N*-Methylphenethylamino)-acetic acid isopropyl ester (14f). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14f**); 1.25 (d, 6H, J=6.0 Hz, CH_3), 2.46 (s, 3H, NCH_3), 2.73–2.85 (m, 4H, CH_2N and CH_2Ar), 3.29 (s, 2H, CH_2CO), 5.03–5.11 (m, 1H, OCH), 7.18–7.22 (m, 3H, ArH), 7.24–7.31 (m, 2H, ArH); IR (film) 1739, 1454, 1176 cm^{-1}; m/z (ES$^+$); 236 (MH$^+$); HRMS 236.1643 (MH$^+$), $C_{14}H_{22}NO_2$ requires 236.1645.

4.2.10. (*N*-Methylphenethylamino)-acetic acid cyclohexyl ester (14g). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14g**); 1.20–1.93 (m, 10H, CH_2), 2.44 (s, 3H, NCH_3), 2.73–2.85 (m, 4H, CH_2N and CH_2Ar), 3.28 (s, 2H, CH_2CO), 4.88–4.93 (m, 1H, OCH), 7.18–7.22 (m, 3H, ArH), 7.24–7.31 (m, 2H, ArH); IR (film) 1740, 1452, 1172 cm^{-1}; m/z (ES$^+$); 276 (MH$^+$); HRMS 276.4029 (MH$^+$), $C_{17}H_{26}NO_2$ requires 276.4023.

4.2.11. (*N*-Methylphenethylamino)-*N*-propyl acetamide (14h). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14h**); 0.83 (t, 3H, J=7.5 Hz, CH_3), 1.38 (S$_e$, 2H, J=7.5 Hz, CH_2), 2.35 (s, 3H, NCH_3), 2.69 (t, 2H, J=6.5 Hz, CH_2Ar), 2.76 (t, 2H, J=6.5 Hz, CH_2N), 3.00–3.08 (m, 4H, CH_2CO and CH_2N), 6.80 (s, br, 1H, NH), 7.17–7.31 (m, 5H, ArH); IR (film) 1662, 1527, 1454, 1148 cm^{-1}; m/z (ES$^+$); 235 (MH$^+$); HRMS 235.1813 (MH$^+$), $C_{14}H_{23}N_2O$ requires 235.1805.

4.2.12. (*N*-Methylphenethylamino)-*N*-allyl acetamide (14i). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14i**); 2.37 (s, 3H, NCH_3), 2.66–2.79 (m, 4H, CH_2Ar and CH_2N), 3.04 (s, 2H, CH_2CO), 3.70 (t, 2H, J=5.5 Hz, CH_2N), 5.06–5.09 (m, 2H, =CH_2), 5.64–5.72 (m, 1H, =CH), 6.89 (s, br, 1H, NH), 7.16–7.31 (m, 5H, ArH); IR (film) 1664, 1521, 1454, 1275 cm^{-1}; m/z (ES$^+$); 233 (MH$^+$); HRMS 233.1654 (MH$^+$), $C_{14}H_{21}N_2O$ requires 233.1649.

4.2.13. (*N*-Methylphenethylamino)-*N*-benzyl acetamide (14j). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H

(**14j**); 2.35 (s, 3H, NCH_3), 2.66–2.73 (m, 4H, CH_2Ar and CH_2N), 3.08 (s, 2H, CH_2CO), 4.27 (d, 2H, J=6.0 Hz, ArCH_2N), 7.08–7.33 (m, 10H, ArH); IR (film) 1668, 1520, 1496, 1454, 1265, 1123 cm^{-1}; m/z (ES$^+$); 283 (MH$^+$); HRMS 283.1814 (MH$^+$), $C_{18}H_{23}N_2O$ requires 283.1805.

4.2.14. (*N*-Methylphenethylamino)-*N*-phenethyl acetamide (14k). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14k**); 2.28 (s, 3H, NCH_3), 2.62–2.72 (m, 6H, CH_2Ar, CH_2Ar and CH_2N), 2.98 (s, 2H, CH_2CO), 3.31 (q, 2H, J=6.5 Hz, CH_2N), 6.87 (s, br, 1H, NH), 7.11–7.31 (m, 10H, ArH); IR (film) 1668, 1524, 1454, 1124 cm^{-1}; m/z (ES$^+$); 297 (MH$^+$); HRMS 297.1971 (MH$^+$), $C_{19}H_{25}N_2O$ requires 297.1961.

4.2.15. (*N*-Methylphenethylamino)-*N*-cyclohexyl acetamide (14l). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14l**); 0.98–1.83 (m, 10H, CH_2), 2.33 (s, 3H, NCH_3), 2.66–2.82 (m, 4H, CH_2N and CH_2Ar), 3.04 (s, 2H, CH_2CO), 3.63–3.72 (m, 1H, NCH), 6.87 (s, br, 1H, NH), 7.18–7.33 (m, 5H, ArH); IR (film) 1668, 1520, 1452, 1150, 1053 cm^{-1}; m/z (ES$^+$); 275 (MH$^+$); HRMS 275.2113 (MH$^+$), $C_{17}H_{27}N_2O$ requires 275.2118.

4.2.16. *N*-Methoxy-2-(*N*-methylphenethylamino)-acetamide (14m). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14m**); 0.36 (s, 3H, NCH_3), 2.68 (t, 2H, J=6.0 Hz, CH_2Ar), 2.75 (t, 2H, J=6.0 Hz, CH_2N), 3.09 (s, 2H, CH_2CO), 3.59 (s, 3H, OCH_3), 7.18–7.34 (m, 5H, ArH), 8.86 (s, br, 1H, NH); IR (film) 1673, 1495, 1455 1124, 1080, 1050 cm^{-1}; m/z (ES$^+$); 223 (MH$^+$); HRMS 223.1435 (MH$^+$), $C_{12}H_{19}N_2O_2$ requires 223.1441.

4.2.17. [2-(*N*-Methylphenethylamino)-acetylamino]-acetic acid methyl ester (14n). As a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (**14n**); 2.40 (s, 3H, NCH_3), 2.71 (t, 2H, J=6.5 Hz, CH_2Ar), 2.78 (t, 2H, J=6.5 Hz, CH_2N), 3.07 (s, 2H, CH_2CO), 3.73 (s, 3H, OCH_3), 3.84 (d, 2H, J=6.0 Hz, CH_2COCH$_3$), 7.18–7.32 (m, 5H, ArH); IR (film) 1752, 1673, 1524, 1454, 1437, 1206, 1128 cm^{-1}; m/z (ES$^+$); 265 (MH$^+$); HRMS 265.1539 (MH$^+$), $C_{14}H_{21}N_2O_3$ requires 265.1547.

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