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One-pot Hofmann elimination–transesterification/amidation reactions on REM resin using perfluorous solvents

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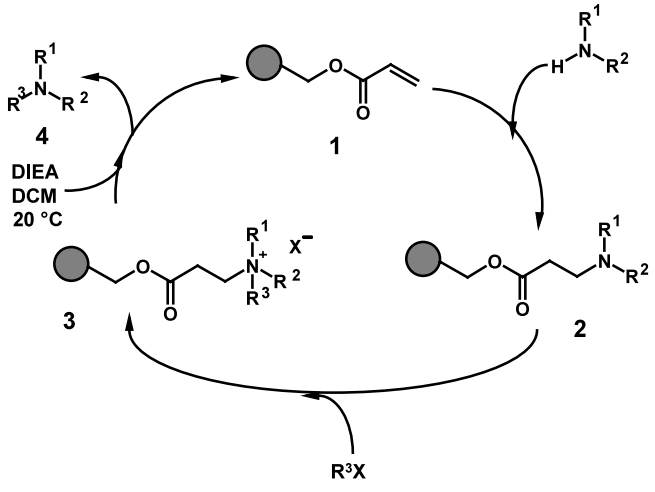
Abstract—The incorporation of 2,2,2-trifluoroethanol esters into substrates for the REM resin synthesis of 3° amines allows a one-pot Hofmann elimination/transesterification protocol to be performed. In this way α-amino acid esters and amides were synthesised by adding alcohols or 1° amines to the Hofmann elimination mixture. The excess of nucleophile required to drive the transesterification or amidation to completion was found to be considerably lower when perfluorous solvents were used to accelerate the reaction (FAST effect). © 2002 Elsevier Science Ltd. All rights reserved.

The use of solid-phase organic synthesis (SPOS) as a tool for the synthesis of chemical libraries is an area of great importance, both in academia and in the pharmaceutical industry.[1] REM resin methodology is an efficient approach for the solid phase synthesis of 3° amines.[2] 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).

The use of 2,2,2-trifluoroethanol esters as activating groups in peptide coupling and transesterification reactions has been previously reported.[3,4] It was thought that by incorporating such a moiety into the alkyl halide used for quaternisation, a 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.

In order to test this hypothesis REM resin bound *N*-methylphenethylamine **5** was quaternised with halide **6** (20 equiv., DMSO, 20°C, 1 h) and subjected to Hofmann elimination conditions (DIPEA 2 equiv., K_2CO_3 2 equiv., DCM) in the presence of methanol (Scheme 2, X = O, R = CH_3).[5] The results are shown in Table 1.

For reactions in DCM, although transesterification did occur, the process did not proceed to completion with less than 30 equiv. of methanol (Table 1, entries 1–5). In order to reduce this prohibitive excess, reaction was attempted in perfluorohexane. We have recently reported large increases in yield for solid-phase Michael reactions with this solvent due to its immiscibility with common reagents and a consequent reagent concentra-



Scheme 1.

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

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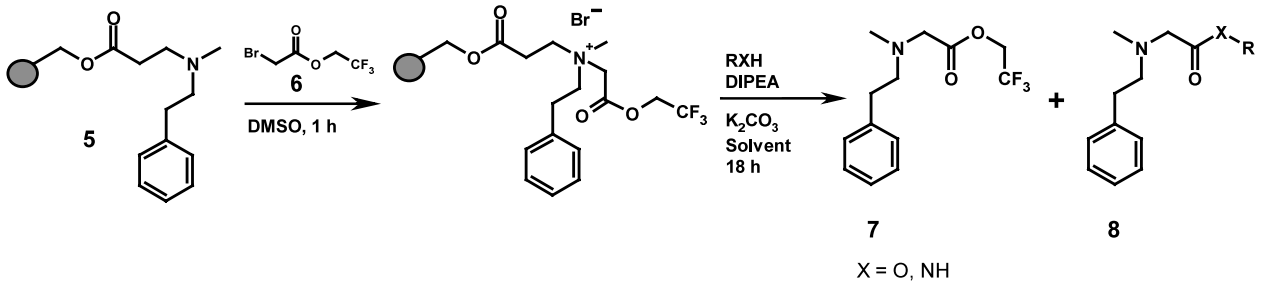


Scheme 2.

Table 1.[a]

Entry	Solvent	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	Perfluorohexane	2	>95
7	Perfluorohexane	5	>95

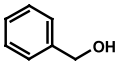
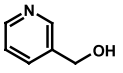
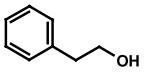
[a] Quaternisation (0.05 mmol resin, 1 mmol **6**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIPEA 2 equiv., K_2CO_3 4 equiv., MeOH, solvent 1 mL). For procedure see Ref. 6.
[b] Conversion determined by ^{1}H NMR ($CDCl_3$).

tion effect.[2c] Use of this solvent did indeed result in improvements with only traces of trifluoroester **7** seen with 2 equiv. of methanol and only product **8** observed when 5 equiv. were used (Table 1 entries 6–7). No transesterification was observed under any conditions when the 2,2,2-trifluoroethanol ester was replaced with an ethyl ester.

It was conceivable that the increases in conversion seen with perfluorohexane were simply due to the miscibility of the liberated 2,2,2-trifluoroethanol with the perfluorous solvent and the favourable effects this would have on the transesterification equilibrium. 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 2). All of the 1° alcohols studied gave complete transesterification when reaction was performed in perfluorohexane with generally less than 50% conversion in DCM. With 2° alcohols the reaction did not proceed to completion with either solvent (Table 2, entry 7) although once again conversions in perfluorohexane were considerably higher than in DCM.

The use of 1° amines to give, after Hofmann elimination, α-amino acid amides (Scheme 2, X = NH) was also successful (Table 3). Once again the use of perfluorohexane as solvent gave greater conversions than DCM.

Table 2.[a]

Entry	Alcohol	Equiv.	Solvent	Conversion (%)[b]
1	MeOH	5	DCM	49
			Perfluorohexane	>95
2	EtOH	10	DCM	25
			Perfluorohexane	>95
3		5	DCM	28
			Perfluorohexane	>95
4		2.5	DCM	59
			Perfluorohexane	>95
5		2.5	DCM	39
			Perfluorohexane	>95
6		10	DCM	28
			Perfluorohexane	>95
7		10	DCM	<5
			Perfluorohexane	50

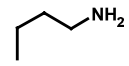
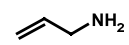
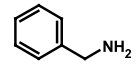
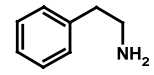
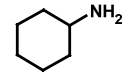
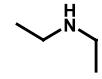
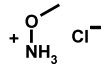
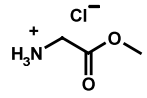
[a] Quaternisation (0.05 mmol resin, 1 mmol **6**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIPEA 2 equiv., K_2CO_3 4 equiv., ROH, solvent). Solvent volume was 1 mL unless otherwise stated. For procedure see Ref. 6.
[b] Conversion determined by ^{1}H NMR ($CDCl_3$).

Although 1° amines reacted efficiently to give the corresponding amide **9**, no product could be detected when 2° amines were used as the nucleophile (Table 3, entry 6). This interesting reactivity could perhaps be exploited in a selective scavenger reagent for primary amines and studies to investigate this possibility are currently underway. Hydroxylamines and α-amino acids were also suitable nucleophiles for the transesterification process (Table 3, entries 7 and 8).

When volatile amines/alcohols were used as nucleophile any excess was simply removed at the end of the procedure by evaporation. Excesses of nucleophile for which this treatment was not amenable were removed by the use of a polymer-supported isocyanate (for amines),[7] or sulphonyl chloride (for alcohols)[8] scavenger reagent.

In summary, the incorporation of a 2,2,2-trifluoroethanol ester into substrates for REM resin

Table 3.[a]

Entry	Amine	Equiv.	Solvent	Conversion (%)[b]
1		5	DCM	88
			Perfluorohexane	>95
2		5	DCM	78
			Perfluorohexane	>95
3		5	DCM	88
			Perfluorohexane	>95
4		5	DCM	>95
			Perfluorohexane	>95
5		20	DCM	20
			Perfluorohexane	83
6		20	DCM	<5
			Perfluorohexane	<5
7		5	DCM	50
			Perfluorohexane and DCM (0.1 mL)	88
8		5	DCM	17
			Perfluorohexane and DCM (0.1 mL)	81

[a] Quaternisation (0.05 mmol resin, 1 mmol **6**) performed for 1 h in DMSO. Transesterification performed for 18 h (0.05 mmol resin, DIPEA 2 equiv., K_2CO_3 4 equiv., RNH_2, solvent). Solvent volume was 1 mL unless otherwise stated. For procedure see Ref. 6.

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

chemistry allows a one-pot Hofmann elimination–transesterification process to be performed as the last step in the reaction cycle. This would allow the synthesis of a wide variety of amino acid esters and amides from a single batch of quaternised resin by splitting at the Hofmann elimination stage and treating with a variety of alcohols and 1° amines. The extent of transesterification/amidation was found to be greatest when perfluorohexane was used as the solvent. These results represent another manifestation of the so-called FAST (fluorocarbon accelerated supported transformation) effect which we have previously reported for Michael additions.[2c] Hence this technique is potentially useful for accelerating a broad range of solid supported transformations.

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5. REM resin was prepared according to the published procedure,[2b] with a 1% PS-DVB resin matrix. REM resin loading was 1.23 mmol/g.
6. *Typical reaction conditions*: REM resin bound *N*-methylphenethylamine (0.05 mmol) was suspended in DMSO (1 mL) and treated with **6** (1 mmol). The mixture was shaken at 20°C for 1 h, filtered, washed (3×1 mL DMF, DCM) and dried in vacuo. The resin was then treated with the nucleophile (0.125–1 mmol), K_2CO_3 (0.2 mmol), DIPEA (0.1 mmol) and the appropriate solvent and shaken at 20°C for 18 h. The product was then isolated by filtration and resin washing (1×1 mL DCM, 3×1 mL 1:1 v/v toluene/hexane, DCM).
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