



Fluorocarbon accelerated supported transformations (FAST) on REM resin

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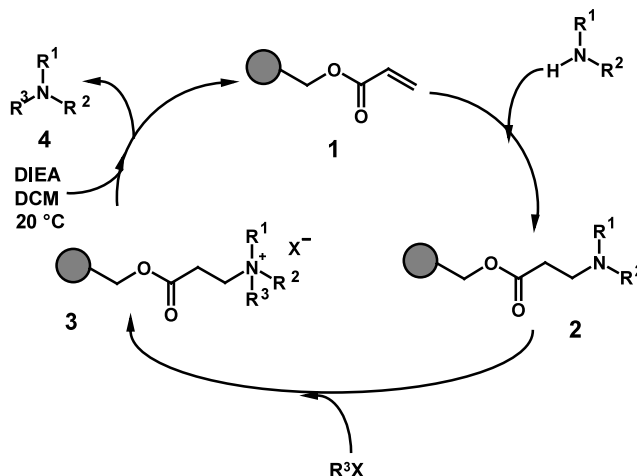
Abstract—The use of perfluorous organic solvents in the solid-phase synthesis of 3° amines on REM resin allows a large reduction in both reaction time and the amount of amine required for a successful Michael reaction. Yields of products were typically at least three fold greater than those observed with standard solvents under the same conditions. © 2001 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 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 in the case of costly or commercially unavailable reagents. Perfluorous organic solvents are well known for their immiscibility with common organic solvents,² and it was thought that the use of such perfluorous entities in SPOS may result in a ‘reagent concentration effect’ by confining reagents solely to the interior of the polymer bead. In this way the amount of reagent required and/or reaction time could be reduced. We have termed this concept Fluorocarbon Accelerated Supported Transformations (FAST). In addition, the immiscibility of the perfluorous solvents would make their separation from organic effluent and reuse possible. The use of perfluorous solvents to accelerate solution phase Diels–Alder reactions via a fluorophobic interaction has been previously reported.³ Herein we present our results using the FAST concept in the synthesis of 3° amines on REM resin.

REM resin methodology is an efficient approach for the solid-phase synthesis of 3° amines.⁴ 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).

It was thought that the reagent concentration effect could impact on both the Michael addition (**1**→**2**) and quaternisation (**2**→**3**) stages of the reaction cycle, both requiring 5–10 equiv. of reagent and overnight reaction in *N,N*-dimethylformamide (DMF). Our initial efforts were concentrated on the Michael addition. REM resin **1** (polystyrene with 1% divinylbenzene crosslinking, 2 mmol/g) was suspended in various solvents in the pres-



Scheme 1.

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

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ence of amine **5**, **6** or **7** (2 equiv.) at 20°C for 3 h (Scheme 2). This was followed by standard quaternisation (BnBr 10 equiv., DMF, 18 h) and cleavage (DIPEA 2 equiv., DCM, 6 h) to give the expected products **8**, **9** and **10**.^{4b,5} The yields are shown in Table 1. Product purities were effectively unchanged regardless of solvent and were greater than 90% as determined by HPLC.

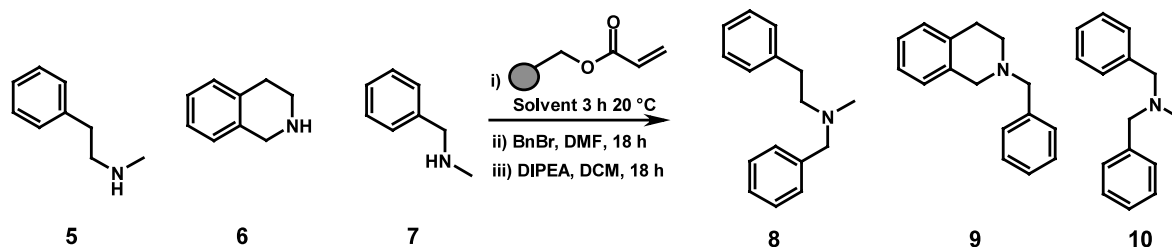
For Michael reaction, as anticipated, aliphatic perfluorous solvents gave appreciably greater yields than the standard DMF, which failed to give any product under these conditions (Table 1, entry 1 versus entries 10–13). Interestingly, aromatic perfluorous solvents did not give any product. When perfluorohexane 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 for use of the same amount of solvent alone (Table 1, entries 14, 15 versus entries 2 and 4) and similar to that seen when a large excess of amine was used as solvent (Table 1, entry 5). The use of co-solvents was thought to increase yields by providing a highly concentrated solution of reagent within the resin beads. The level of increase in yield was particularly startling when it is considered that the resins used showed little or no swelling in any of the perfluorous solvents. The use of other solvents in which

amine solubility and resin swelling were also poor gave no product (Table 1, entries 6 and 7).

Having established the feasibility of using perfluorous solvents in the Michael reaction the effect on yield of the amount of amine used was investigated (Table 2). Here amine **5** was added in varying amounts to REM resin and agitated at 20°C for 2 h before standard quaternisation with benzyl bromide and cleavage. Once again a clear improvement in yield when perfluorous solvents were used is apparent with all such reactions showing effectively quantitative conversion with only 4 equiv. of amine after 2 h. Conversely, under standard conditions complete Michael reaction did not occur with even 20 equiv. of amine **5**. Using no solvent, the reaction could be forced to completion in 2 h but only with the use of 20 equiv. of amine. Similar excesses were required (15–20 equiv.) when small amounts of DMSO and DMF were used as solvent.

Finally, the effect of increasing non-fluorous co-solvent volume on yield was evaluated (Table 3). The rationale behind such an investigation was to determine the optimal amount of solvent.

It was thought that, as volume of solvent increased, the reagent concentration effect may become attenuated



Scheme 2.

Table 1. ^a

Entry	Solvent ^b	Yield ^c (%) 8	Yield ^c (%) 9	Yield ^c (%) 10
1	DMF	<5	<5	<5
2	DMF (0.03 ml)	29	7	10
3	DMSO	<5	<5	<5
4	DMSO (0.03 ml)	24	20	24
5	Neat amine ^c	96	94	95
6	Water	<5		
7	Methylcyclohexane	<5		
8	Hexafluorobenzene	<5		
9	Octafluorotoluene	<5		
10	Perfluorodecalin	58		
11	Perfluorotripropylamine	65		
12	Perfluoromethylcyclohexane	46		
13	Perfluorohexane	57	41	36
14	Perfluorohexane and 0.03 mL DMSO ^d	88	49	54
15	Perfluorohexane and 0.03 mL DMF ^d	94	80	72

^a Michael reaction performed for 3 h. For procedure see Ref. 5.

^b All reactions performed with 0.05 mmol resin and 0.1 mmol amine. Solvent volume was 1 mL unless otherwise stated.

^c Approx. 150 equiv. amine used as solvent.

^d Represents the use of a standard amount (1 mL) of perfluorohexane with 0.03 mL DMSO/DMF.

^e Yields determined by ¹H NMR using *N*-methylmaleimide as an internal standard.

Table 2. ^a

Equiv. amine 5	Yield (%) ^b						
	No solvent ^c	DMF ^d	DMF (0.03 mL)	DMSO (0.03 mL)	Perfluorohexane ^d	Perfluorohexane and DMF ^e (0.03 mL)	Perfluorohexane and DMSO ^e (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

^a Michael reaction performed for 2 h. For procedure see Ref. 5.

^b Yields determined by ¹H NMR using *N*-methylmaleimide as an internal standard.

^c Amine was pipetted onto dry resin.

^d All reactions performed with 0.05 mmol resin in 1 mL solvent unless otherwise stated.

^e Represents the use of a standard amount (1 mL per 0.05 mmol resin) of perfluorohexane with 0.03 mL DMSO/DMF.

Table 3. ^a

Volume of DMF added (μ L)	Yield (%) ^b	
	DMF only ^c	Perfluorohexane and DMF ^d
10	18	76
30	12	75
50	<5	76
100	<5	64
200	<5	60
300	<5	30
500	<5	10
1000	<5	<5

^a Michael reaction (0.05 mmol resin, 0.1 mmol amine) performed for 2 h. For procedure see Ref. 4.

^b Yields determined by ¹H NMR using *N*-methylmaleimide as an internal standard.

^c Michael reaction performed in DMF.

^d Michael reaction performed in perfluorohexane (1 mL) with the stated amount of DMF added.

until the yield observed would be the same as that seen for the same amount of co-solvent alone. As expected, on increasing the solvent volume the yield of tertiary amine product decreased as reagent concentration decreased. This was seen when DMF was the sole solvent, where product could not be detected at solvent volumes above 30 μ L. Where DMF was used as a co-solvent with perfluorohexane, decreases in yield were also seen although reasonable yields were maintained with solvent volumes of up to 200 μ L. This may have implications for other reactions where appreciable volumes of co-solvent are required to solubilise reagents.

In summary, the adoption of perfluorous solvents in the Michael reaction on solid-phase has resulted in a greater than ten fold increase in yield compared to the standard solvent system (DMF). Such increases can be

translated into a reduction of reaction time or a reduction in the excess of reagent required to drive the reaction to completion. The large increases in yield seen are thought to arise from a reagent concentration effect, whereby the reagents become trapped inside the resin bead as a result of their immiscibility in the perfluorous solvents. Our preliminary studies showed a similar effect for perfluorous solvents in the quaternisation step of the REM resin cycle. Further studies investigating the scope of the FAST concept are currently underway and will be reported in due course.⁶

References

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5. *Typical reaction conditions*: REM resin (0.05 mmol) was treated with the appropriate solvent and amine. The mixture was then shaken at rt for 2–3 h, filtered and washed (3 \times 1 mL DMF, DCM, MeOH). The resin was then treated with DMF (1 mL) and benzyl bromide (0.5 mmol), agitated at rt for 18 h, filtered and washed as above. The product was then cleaved by treatment with DIEA (0.1 mmol) and K₂CO₃ (0.4 mmol) in DCM (1 mL), and agitation at rt for 6 h after which the product was isolated by filtration and resin washing (3 \times 1 mL DCM).
6. During the preparation of this manuscript a preliminary report dealing with an increase in rate seen for a polymer supported hydrogenation catalyst with perfluorous solvents was published: Vinson, S. L.; Gagne, M. R. *Chem. Commun.* **2001**, 1130–1131.