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Low dilution procedures in solid-phase organic synthesis: Diels–Alder and Heck reactions

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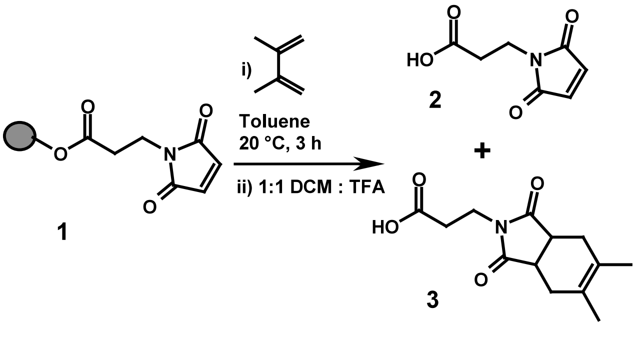
Abstract—The use of extremely low solvent volumes (2 μL or less per mg resin) results in significant increases in yield for both the Diels–Alder and Heck reactions on solid-phase compared to standard high dilution techniques. © 2002 Elsevier Science Ltd. All rights reserved.

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] In such a synthesis a polymer bound substrate is typically swollen in a compatible solvent and treated with an excess of reagents in order to effect a transformation prior to cleavage from the solid support into solution. We have recently reported successes in SPOS by using polar solvents or perfluorous solvents to confine reagents within the polymer support.[2,3] With these techniques poor solubility in the solvent used resulted in preferential partitioning of the reagents within the polymer and so a much higher local concentration of reagents was seen at the functionalised sites of the solid-phase leading to increases in reaction rate. These observations led us to hypothesise that reducing the amount of solvent typically used in a solid-phase synthesis could bring about a similar reagent concentration effect. Herein we report our observations on the effect of low solvent volumes for two reactions commonly performed on solid-phase, the Diels–Alder reaction and the Heck reaction.

The Diels–Alder reaction is one of the most popular processes for forming six-membered rings and both solution and solid-phase examples have been reviewed.[4,5] In order to evaluate the suitability of this reaction to low dilution techniques polymer bound dienophile **1** was prepared by a Mitsunobu reaction between Wang resin and *N*-maleoyl-β-alanine.[6] This was then exposed to 2,3-dimethyl-1,3-butadiene, the substrate cleaved from the Wang resin (Scheme 1) and the extent of reaction evaluated by ^{1}H NMR analysis (Table 1).

Reaction of **1** (94 mg) with 2 equiv. of diene gave a 17% conversion to the product under standard dilution conditions (1 mL) whilst with 0.1 and 0.05 mL of solvent conversion is approximately 70% (Table 1, entry 1 versus entries 2 and 3). When 5 equiv. of the diene was used a similar trend was observed with 33% conversion with 1 mL solvent and approximately 90% with solvent volumes between 0.1 and 0.05 mL. At solvent levels of 0.5 mL and above the resin is completely swollen and a separate solvent phase is discernible. These represent the minimum levels of dilution which would routinely be used in SPOS and conversion here is between 30 and 40%. Interestingly, below 0.05 mL conversion rapidly falls off suggesting an optimal solvent volume exists where reagents have sufficient solvent to access all resin sites. Above this figure additional solvent serves only to



Scheme 1.

Keywords: polmyer support; reagent concentration; solid-phase synthesis; low dilution; Diels–Alder; Heck reaction.

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Table 1. [a]

Entry	Toluene volume (mL)	Diene (equiv.)	Conversion (%)[b]
1	1	2	17
2	0.1	2	70
3	0.05	2	77
4	1	5	32
5	0.9	5	33
6	0.8	5	38
7	0.7	5	39
8	0.6	5	41
9	0.5	5	42
10	0.4	5	53
11	0.3	5	62
12	0.2	5	75
13	0.1	5	90
14	0.075	5	90
15	0.05	5	93
16	0.025	5	76
17	0	5	<5

[a] Diels–Alder reaction (0.05 mmol **1**, 0.53 mmol/g, 94 mg) performed for 3 h in toluene. For procedure see Ref. 9.

[b] Conversion determined by ^{1}H NMR analysis (DMSO).

Table 2.

Entry	DMF volume (mL)	Reaction time (h)	Conversion (%)[b]
1	1	2	40
2	0.05	2	79
3	1	4	46
4	0.5	4	67
5	0.4	4	70
6	0.3	4	71
7	0.2	4	78
8	0.1	4	80
9	0.05	4	89
10	0.025	4	54
11	0	4	<5
12	1	18	54
13	0.1	18	>95
14	0.05	18	>95

[a]Heck reaction (0.05 mmol **4**, 1.06 mmol/g, 47 mg) performed in DMF (ethyl acrylate 2 equiv., $Pd_2(dba)_3$ 0.1 equiv., Et_3N 5 equiv.). For procedure see Ref. 13.

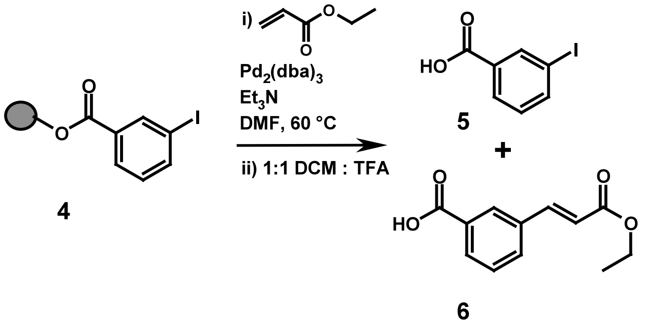
[b]Conversion determined by ^{1}H NMR analysis (DMSO).

dilute the reagent solution and so slows the rate of reaction. The apparent optimal volume for the transformation **1**–**3** is 0.05 mL. When the volume of the diene is taken into account this gives a liquid amount of approximately 0.8 μL per mg of resin. A wide variety of solvent amounts for polymer supported Diels–Alder reactions which have been reported, ranging from 2.6 to 50 μL per mg of resin.[7,8]

The Heck reaction is a commonly used protocol for the coupling of aryl halides and pseudo halides with olefins and its use in solution and on solid-phase has been reviewed.[5b,c,10] In order to investigate the effect of low solvent volume techniques on this reaction, 3-iodobenzoyl chloride was coupled to Wang resin in the presence of DIEA.[11] The resulting aryl halide **4** (47 mg) was then coupled to ethyl acrylate using the Heck reaction before cleavage with TFA/DCM (Scheme 2) and evaluation of the extent of coupling by ^{1}H NMR analysis (Table 2).

As with the Diels–Alder reaction there was a marked improvement in conversion seen at low solvent volumes despite the presence of a solid catalyst which presumably must be dissolved for efficient reaction. Thus, after reaction at 60°C for 2 h at standard dilution (1 mL) a conversion of 40% was observed compared to approximately 80% when only 0.05 mL solvent was used (Table 2, entry 1 versus entry 2). This trend was repeated after reaction for 4 and 18 h (Table 2, entries 3, 9, 12 and 13) with complete reaction after 18 h for low solvent volumes and only 54% conversion under standard dilution conditions. On looking in more detail at the effects of solvent volume (Table 2, entries 3–11) a similar pattern to that seen for the Diels–Alder reaction is observed with solvent volumes below 0.05 mL giving low conversions and those above this figure also leading to poorer levels of reaction. Thus, an optimal solvent volume for the Heck reaction studied appears to be 0.05 mL. When the volume of the reagents used is taken into account this gives a liquid amount of approximately 2 μL per mg of resin. This level, which is higher than that seen for the Diels–Alder reaction may simply reflect the extra solvation requirements of the solid catalyst compared with the all liquid Diels–Alder reagents. Solvent levels of 15 μL per mg of resin have been reported for polymer supported Heck reactions.[12]

In summary, the use of low solvent volumes in both the solid-phase Diels–Alder and Heck reactions has resulted in large increases in yield for these processes. Studies on the effect of solvent volume on both reactions showed the existence of an optimal volume where reagents have sufficient solvent to access all resin sites. Above and below this figure reaction is not as efficient. The optimal amount of solvent indicated represented 2 μL of solvent or less per mg resin, significantly less than that required to totally swell the resin used and give a separate solvent phase. We are currently studying further applications of this effect and will report our findings in due course.



Scheme 2.

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13. *Typical reaction conditions for the Heck reaction*: Wang resin bound 3-iodobenzoic acid (0.05 mmol) was treated sequentially with $Pd_2(dba)_3$ (0.005 mmol), Et_3N (0.25 mmol), DMF (0–1 mL) and ethyl acrylate (0.1 mmol). The suspension was then flushed with argon, shaken at 60°C for 2–18 h, filtered and washed (3×1 mL DCM, 4:1 v/v DMF/H_2O, DMF, DCM, MeOH). The resin was then suspended in DCM/TFA (1 mL, 1:1 v/v) and shaken at 20°C for 1 h. The product was isolated by filtration and resin washing (3×1 mL DCM, 9:1 v/v DCM/MeOH).