A Cleaner Approach to Solid-Supported Radical Chemistry: Application of Hypophosphite Salts to Intramolecular C-C Bond Formation on the Solid-Phase

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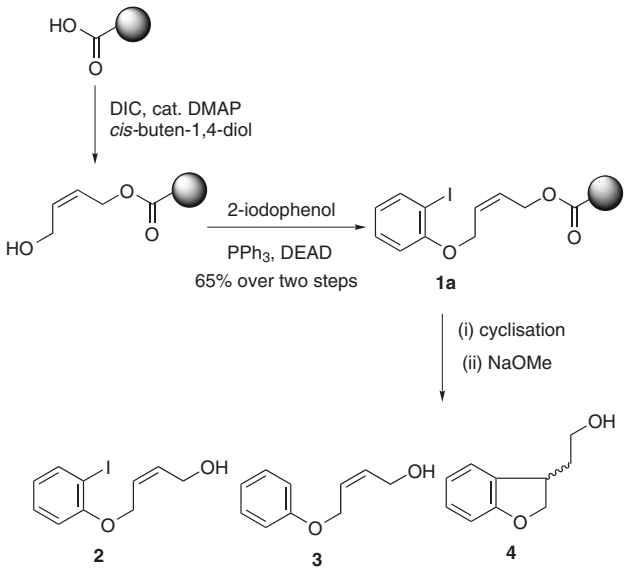
Abstract: The application of hypophosphite salts to solid-supported radical chemistry has been explored. EPHP-mediated intramolecular cyclisations have been shown to give good yield of cyclised products on *J*anda*J*el® resin.

Key words: solid-phase, cyclizations, radical reactions

Organotin hydride-mediated radical chemistry is a particularly powerful method of forming carbon-carbon bonds both in solution[1] and on the solid-phase.[2] However, the well-established neurotoxicity of organotin reagents[3] has precluded their use in the solid-phase synthesis of drug candidate libraries by the pharmaceutical industry. Solution-phase alternatives to organotin hydrides have included silicon-based radical chain carriers such as tris(trimethylsilyl)silane,[4] but cost and ease of oxidation has prohibited the widespread use of this reagent in solid-phase library synthesis. More recently, the application of phosphorous centred radicals (derived from H_3PO_2 salts)[5] to intramolecular C-C bond formation has been demonstrated in the solution-phase in a variety of cleaner solvents such as ethanol[6] and water.[7] The application of these cost effective, non-toxic phosphorous reagents to solid-supported radical chemistry would enable library syntheses to utilize radical-mediated bond formation without the problem of potential contamination of library members with toxic organotin residues.

Herein we report our preliminary work towards developing a cleaner approach to solid-supported radical chemistry by exploring the application of hypophosphite salts to a representative solid-phase intramolecular radical reaction on a variety of commercially available resins.

As hypophosphite reagents had not previous been used to effect resin supported radical reactions we chose to test the reagents on a simple system that had been shown to undergo efficient radical cyclisation on the solid-phase.[2a,c] Iodoether radical precursor **1a** was synthesised on 2% divinylbenzene cross-linked carboxypolystyrene (1.34 mmol/g, Novabiochem) via a solid-phase Mitsunobu reaction[8] (Scheme 1)**.** The loading of **1a** was 0.63 mmol/g as determined by iodine elemental analysis. The resin-bound radical precursor **1a** was treated with two commercially available radical chain carriers, *N*-ethylpiperidine hypophosphite (EPHP)[9] and tributyltin hydride (Bu_3SnH) in anhydrous, degassed toluene under reflux. In all reactions varying amount of cyclised product, benzofuran **4** was detected by HPLC analysis of the resin cleavage mixtures after reaction[10] (Table 1).



Scheme 1 Synthesis of iodoether **1a** on carboxypolystyrene resin

Table 1 Cyclisation of Resin-Bound Iodoether **1a** in Toluene with Bu_3SnH (10 equiv) or EPHP (20 equiv)

Time (h)	Chain carrier[a]	AIBN (equiv)[a]	Yield of **2** (%)[b]	Yield of **3** (%)[b]	Yield of **4** (%)[b]
4	Bu_3SnH	1	4	1	95
4	EPHP	1	77	4	19
48	EPHP	3[c]	38	5	57
18	EPHP	3[d]	58	Trace	42

[a] Equivalents are based on the initial loading of resin-bound iodoether **1a**.
[b] Ratio determined by HPLC analysis of reaction mixture after cleavage from the resin.
[c] 3 Equiv of initiator based on the initial loading of resin-bound iodoether **1a**, 1 equiv added at t = 0 h, t = 18 h and t = 36 h.
[d] Drop-wise addition of AIBN over 18 h.

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Cyclisation with EPHP was sluggish compared to Bu_3SnH with only 57% conversion after 48 hours even with the addition of three equivalents of AIBN.

It was noted that the EPHP salt was not soluble in toluene so a variety of solvent systems were screened as alternatives, in these systems the resin was in a swollen state and the EPHP salt in solution. The reactions were performed with either AIBN or V-50[11] as the radical initiator. In all cases the conversion to benzofuran **4** was not significantly improved (Table 2).

Table 2 Cyclisation of Resin-Bound Iodoether **1a** with EPHP (20 equiv) and AIBN or V-50 (1 equiv)

Solvent	Time (h)	Yield of **2** (%)[a]	Yield of **3** (%)[a]	Yield of **4** (%)[a]
Toluene	4	77	4	19
THF–H_2O (4:1)	4	99	Trace	1
THF–H_2O (4:1)[b]	4	98	Trace	2
THF–EtOH (4:1)	4	78	2	20
THF–EtOH (4:1)[c]	48	31	6	63

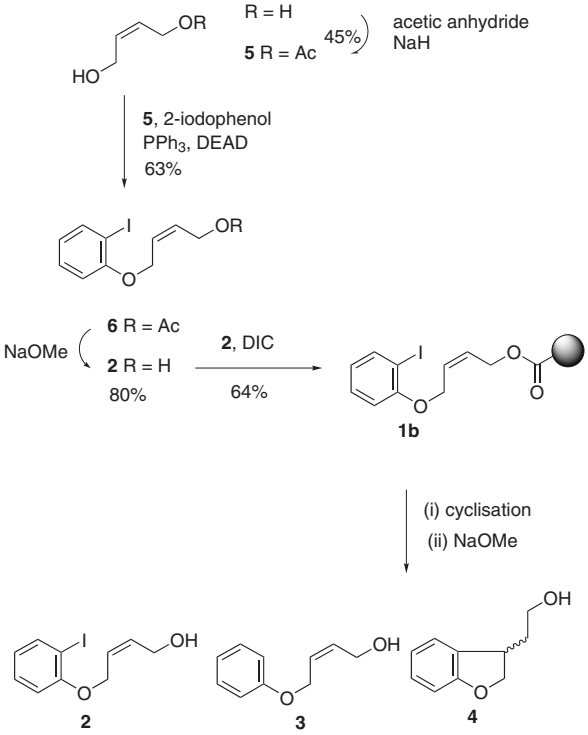
[a] Ratio determined by HPLC analysis of reaction mixture after cleavage from the resin.
[b] Initiator V-50 (1 equiv).
[c] 3 Equiv of initiator based on the initial loading of resin-bound iodoether **1a**, 1 equiv added at t = 0 h, t = 18 h and t = 36 h.

As EPHP is a salt the sluggish reaction on divinylbenzene cross-linked polystyrene could be due to low concentration of the reagent within the hydrophobic polymer matrix. This prompted us to explore the same reaction on a more hydrophilic resin, NovaSyn® TG carboxy resin (0.25 mmol/g, Novabiochem).

The use of this resin could also potentially allow the cyclisation to be carried out in less toxic solvents such as water or ethanol, which do not swell divinylbenzene cross-linked polystyrene resins. The radical precursor **2** was synthesized in solution[12] and loaded onto NovaSyn® TG carboxy resin via an esterification reaction to give the resin-bound radical precursor **1b** (Scheme 2). The loading of **1b** was 0.15 mmol/g as determined by iodine elemental analysis. Radical precursor **1b** was treated with EPHP and either AIBN or V-50 in a variety of solvents (Table 3).

The EPHP mediated reactions (Table 3, entries 2–6) ranged from 0% to 89% conversion with reduced product **3** detected in all cases. In comparison, reaction with tributyltin hydride and AIBN gave 97% conversion to benzofuran **4** (Table 3, entry 1) with only a trace amount of the reduced product **3** detected.

In order to explore the influence of the solid-support on the product ratio of the EPHP-mediated cyclization, iodoether **2** was loaded onto a variety cross-linked and PEG grafted solid-supports[14] then subjected to radical cyclization.[15] After reaction cleaved material was analysed by HPLC (Table 4).



Scheme 2 Synthesis of iodoether **1b** on NovaSyn® TG carboxy resin

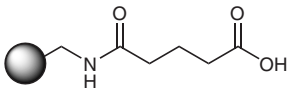
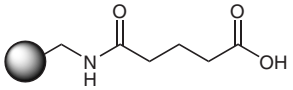
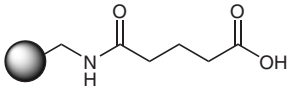
Table 3 Cyclisation of NovaSyn® TG-Bound Iodoether **1b** with either Bu_3SnH (10 equiv)/AIBN (1 equiv) or EPHP (20 equiv)/AIBN or V-50 (1 equiv)

Solvent	Chain carrier	Time (h)	Yield of **2** (%)[a]	Yield of **3** (%)[a]	Yield of **4** (%)[a]
Toluene	Bu_3SnH	4	2	1	97
Toluene	EPHP	18	74	2	24
EtOH	EPHP	18	92	Trace	8
H_2O	EPHP[b]	18	100	0	0
H_2O	EPHP	18	98	Trace	2
THF:EtOH (4:1)[13]	EPHP	18	33	3	64
THF:EtOH (4:1)[c]	EPHP	48	5	6	89

[a] Equivalents are based on the initial loading of resin-bound iodoether **1a**.
[b] Initiator V-50 (1 equiv).
[c] An additional equiv of initiator added at 24 h.

Macroporous resin (ArgoPore®) gave a conversion to the cyclised product **4** similar to cross-linked polystyrene but had a higher percentage of reduced product **3**. The PEG grafted resins, HypoGel® and ArgoGel® all resulted in conversion to the cyclised product with similar product distribution to NovaSyn® TG resin. The polytetrahydro-

Table 4 Cyclisation of Resin-Bound Iodoether **2** with EPHP (20 equiv) and Initiator (2 equiv)[a] 48 h in THF–EtOH (4:1)

Solid-support	Yield of **2** (%)	Yield of **3** (%)	Yield of **4** (%)
 ArgoPore® HL 0.84 mmol/g[b]	31	14	55
 HypoGel® 0.54 mmol/g[b]	6	7	87
 ArgoGel®, 0.35 mmol/g[b]	5	7	88
 *J*anda*J*el® 0.32 mmol/g[b]	0	2	98

[a] 1 Equiv added at t = 0 h, 1 equiv added at t = 24 h.
[b] Loading of iodoether, determined by elemental analysis for iodine.

furan cross-linked resin, *J*anda*J*el® gave excellent conversion, with only a small amount of reduced product **3** detected. In order to determine if the optimisation was specific to iodoether **2**, an alternative radical precursor was attached to *J*anda*J*el® resin, a primary radical precursor **7** (Figure 1).

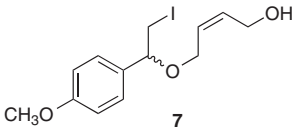


Figure 1

Both **2** and **7** were cyclised using the optimised reaction conditions. The cyclisations were scaled up to allow determination of a crude yield rather than just a conversion to either cyclised or reduced product as had previously been determined (Table 5).

Table 5 Cyclisation of *J*anda*J*el®-Bound Iodoethers

Radical precursor	Crude yield (%)[a]	Purity of cyclised product
2	97	77[b]
7	92	69[b] (2:1, *trans*:*cis*)[c]

[a] Based on the loading of resin-bound iodoether.
[b] Determined by HPLC analysis at 220 nm detection.
[c] Determined by NMR.

In conclusion, it appears from the limited reactions studied that *N*-ethylpiperidine hypophosphite (EPHP) could be used as a cleaner alternative to tributyltin hydride for solid-supported intramolecular radical cyclisation. The choice of polymer support may be critical to the success of the reaction but the cyclisations studied proceed efficiently in THF–EtOH (4:1) on *J*anda*J*el® resin and this may reflect the concentration of EPHP/AIBN within the polymer matrix of this resin. Further studies to explore the partitioning of EPHP within a resin bead and subsequent effects on product ratio of radical cyclisations are in progress.

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(9) Carboxypolystyrene resin loaded with **1a** (100 mg, 0.063 mmol) was suspended in anhyd degassed toluene (1 mL), EPHP (225 mg, 1.26 mmol) and AIBN (10 mg, 0.06 mmol) were added, and then the reaction mixture was heated under reflux for 4 h. The resin was washed with DMF (3 × 5 mL), THF (3 × 5 mL), THF–H_2O (1:1, 3 × 5 mL), THF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL) then dried under vacuum for 48 h.
(10) Resin was suspended in THF–MeOH (4:1), excess MeONa was added and the reaction mixture was agitated for 24 h. The resin was filtered off and the solution was eluted through a plug of ion exchange resin (Dowex 50W-X8 H^+) then analysed by HPLC on a Alltech econosil Si column eluting with hexane–*i*-PrOH (0–5 min 100% hexane, 5–35 min gradient 0–30% *i*-PrOH): iodoether **2**, 18.4 min; benzyl ether **3**, 17.3 min; benzofuran **4**, 19.9 min; 220 nm detection.
(11) 2,2′-azobis(2-amidinopropane) dihydrochloride, a water soluble azo radical initiator.
(12) The stepwise solid-phase synthesis (Scheme 1) could not be applied to NovaSyn® TG carboxy resin as reaction with *cis*-butan-1,4-diol resulted in extensive cross-linking of the resin.

(13) NovaSyn ® TG resin loaded with **1b** (100 mg, 0.015 mmol) was suspended in degassed solvent (0.25 mL), EPHP (54 mg, 0.30 mmol) and AIBN (2.5 mg, 0.015 mmol) or V-50 (4 mg, 0.015 mmol) were added then the reaction mixture was heated under reflux for 18 h. The resin was washed with THF (3 × 5 mL), THF–H_2O (1:1, 3 × 5 mL), THF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL) then dried under vacuum for 48 h.

(14) Carboxy-functionalised resins were either commercially available (HypoGel®) or synthesized from commercially available amino functionalised resin by reaction with glutaric anhydride (*J*anda*J*el®, ArgoGel® and ArgoPore®).

(15) The reactions were performed on 100 mg of resin and the amount of solvent used in the reaction was dependent on the loading of the resin (100 mg of resin with 1 mmol g^{-1} loading = 1.5 mL solvent for reaction), 1 equiv of initiator added at t = 0 h and t = 24 h.