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Solid-phase synthesis of oligoesters using a *J*anda*J*el™ resin

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Abstract—This communication describes a general method for the solid-phase synthesis of oligomeric esters. A *J*anda*J*el™ resin was utilized as the solid support in conjunction with the highly acid labile Rink linker. Ester coupling reactions were performed using buffered reagents and the monomer was protected as its allyl ester. In this manner, ester coupling and deprotection could be performed under essentially neutral conditions, giving rise to products in both excellent yields and purity.

Since the seminal work of Merrifield for the solid-phase synthesis of oligopeptides,[1] polymer-supported syntheses have been applied to the preparation of other biologically relevant molecules such as oligonucleotides,[2] oligosaccharides[3] and more recently peptidomimetics.[4] Today, solid-phase combinatorial synthesis is the accepted method used in the quest for compounds of pharmaceutical, agricultural or material interest.[5] Oligoesters can be found in several naturally occurring compounds including the depsipeptides valinomycin,[6] onchidin[7] and quinomycin[8] as well as the macrodiolides pyrenophorin, vermiculin and elaphylin.[9] In materials science, polyesters are among the most versatile synthetic polymers and have found wide commercial use as fibers, plastics and coatings.[10] Despite this, the chemical literature contains few examples of the preparation of oligoesters using either conventional solution-phase or solid-phase methodology.[11]

Our own interest in oligo esters stems from recent work that involves 'proof of principle' experiments that have demonstrated the feasibility of antibody catalyzed degradation of such compounds.[12] During these studies we required access to a series of discrete oligoesters type **2a–e** based on the monomer 4-hydroxyphenyl acetic acid **1** (Fig. 1). Indeed, this monomer has been utilized in the preparation of liquid crystalline polymers.[13] Efforts made to prepare these compounds proved difficult since purification was complicated by the presence of incomplete oligoester sequences and the oligoesters lack of solubility. A four-step solution-phase synthesis of a tetrameric ester was achieved in an acceptable 35% overall yield. However, an additional four steps of this sequence to give a hexameric product could only be achieved in 0.4% overall yield.

In order to overcome the problems associated with the purification and solubility of these intermediate sequences, a solid-phase synthetic strategy was devised. Since the desired oligoester had to be cleaved from the resin under very mild conditions, the highly acid labile Rink linker was utilized.[14] This linker was introduced onto chloromethyl functionalized *J*anda*J*el™ resin, (our own high swelling alternative to Merrifield resin),[15] using standard methodology.[16] The dimeric ester **5** was deemed appropriate for the elongation step and was

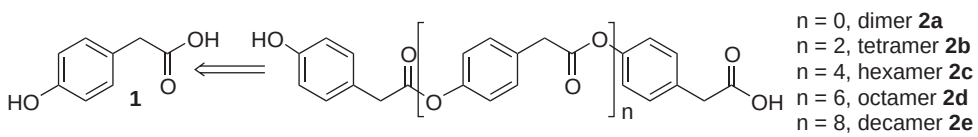

Figure 1.

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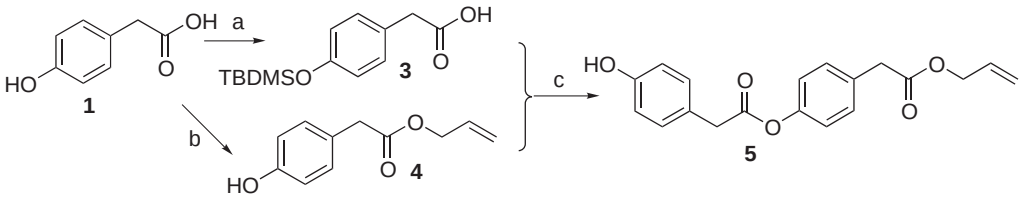
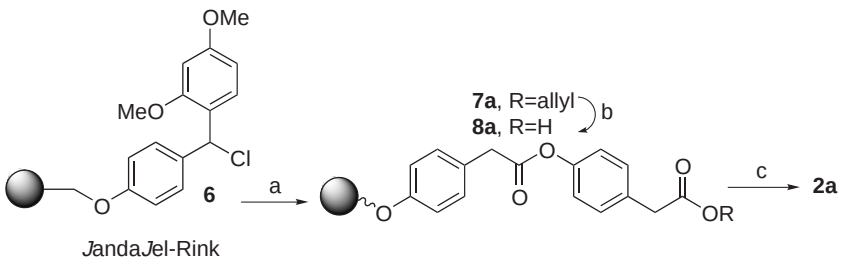
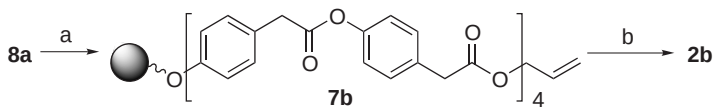


Scheme 1. (a) i. DBU, BnBr, CH_3CN, 75%. ii. TBDMSCl, imdazole, DMF, 98%. iii. H_2, Pd/C, MeOH, EtOAc, 97%. (b) DBU, allyl bromide, CH_3CN, 58%. (c) i. EDC, HOBT, DIPEA, THF, 49%. ii. TBAF, THF, 89%.



Scheme 2. (a) i. **5**, DIPEA, CH_2Cl_2. ii. Ac_2O, Pyr., CH_2Cl_2. (b) $Pd(Ph_3)_4$, $PhSiH_3$, CH_2Cl_2. (c) 10% TFA, CH_2Cl_2.



Scheme 3. (a) **5**, DIC, DMAP, PTSA, CH_2Cl_2. (b) i. $Pd(Ph_3P)_4$, $PhSiH_3$, CH_2Cl_2. ii. 10% TFA, CH_2Cl_2.

synthesized by reaction of 4-*tert*-butyldimethylsiloxy phenylacetic acid **3** with allyl (4-hydroxy) phenylacetate **4** in the presence of EDC and HOBT, followed by TBAF deprotection of the silyl group (Scheme 1).

Dimeric ester **5** was attached to the Rink functionalized *J*anda*J*el™ resin **6** through the phenolic ether linkage formed in the presence of DIPEA. This was followed by capping of the residual hydroxyl groups with acetic anhydride to give support bound allyl ester **7a** (Scheme 2). The allyl ester protecting group was then removed using catalytic $(Ph_3P)_4Pd$ and $PhSiH_3$ scavenger in CH_2Cl_2[17] to give the support bound dimer **8a**. It was anticipated that these mild and essentially neutral conditions would prevent any undesirable side reactions, indeed, cleavage of a small portion of resin using 10% TFA/CH_2Cl_2 gave dimer **2a** in greater than 90% purity as estimated by ^{1}H NMR and HPLC analysis.

The esterification procedure proved more troublesome to optimize. The standard combinations of EDC, HOBT and DIPEA, or DCC, DMAP and 4-methylmorpholine gave undesirable side products in the resin cleaved material. After much effort we found that a mixture of (diisopropylcarbodiimide) DIC, DMAP and PTSA[18] proved to be an ideal combination giving the desired support bound allyl ester **7b**. Subsequent deprotection and cleavage from the resin gave tetramer **2b** in 79% yield and greater than 90% purity as determined by ^{1}H NMR and HPLC. Since the Rink linker employed is highly acid sensitive, the DMAP and PTSA reagents required mixing prior to addition to the resin (Scheme 3).[19]

With these results in hand, hexamer **2c**, octamer **2d** and decamer **2e** were synthesized by repetition of the deprotection and coupling steps. Hexamer **2c** was obtained in reasonable yield with good purity, moreover, this material could be purified further using preparative TLC. Octamer **2e** and decamer **2e** were also isolated in 54 and 47% yield, respectively, in good purity as estimated by TLC analysis. Unfortunately, attempts to further purify these materials led to decomposition of the product; in addition, the poor solubility of these compounds precluded a more precise estimation of purity by HPLC. Each of the compounds were characterized using ^{1}H NMR and HRMS. The results for these reactions are presented in Table 1.

Table 1. Solid-phase synthesis of oligo esters

Oligo ester	% Yield (crude)	% Purity (crude)
Tetramer, **2b**	79	>90[a]
Hexamer, **2c**	63 (54)[b]	86
Octamer, **2d**	54	ND
Decamer **2e**	47	ND

[a] Purity estimated by ^{1}H NMR.
[b] Yield after purification by TLC given in parentheses.

Conclusion

In conclusion, we have demonstrated the utility of the *J*anda*J*el™ resins for the solid-phase synthesis of oligoesters. By utilizing the highly labile Rink linker, buffered coupling reagents and neutral deprotection conditions the desired oligoesters were isolated from the

resin in good yield and high purity. This convenient solid-phase methodology enabled the synthesis of compounds that were previously inaccessible using conventional solution-phase chemistry.

Acknowledgements

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19. Loading of resin: *J*anda*J*el™ Rink chloride **6**, (590 mg, prepared from chloromethyl *J*anda*J*el™, 0.70 mmol g^{-1} Cl), allyl dimer **5** (391 mg, 1.20 mmol), CH_2Cl_2 15 ml and DIPEA (163 μl, 1.2 mmol) were combined and shaken for 16 h. The resin was washed with CH_2Cl_2 and methanol and dried in vacuo to give resin **7a**. Residual hydroxyl linker groups were capped by shaking a suspension of the resin **7a** in CH_2Cl_2 (15 ml) with acetic anhydride (470 μl, 5.0 mmol) and pyridine (360 μl, 4.5 mmol) for 30 minutes followed by washing with CH_2Cl_2 and methanol.
Deprotection: Allyl ether resin **7a** was suspended in CH_2Cl_2 (15 ml), $Pd(Ph_3P)_4$ (63 mg, 0.06 mmol) and $PhSiH_3$ (615 μl, 5.0 mmol) were added and the mixture was shaken under inert atmosphere for 2 hours. The resin was washed with CH_2Cl_2, methanol and dried in vacuo to give **8a**.
Cleavage procedure: Resin **8a** (62 mg) was treated with 10% TFA in CH_2Cl_2 for 5 minutes. The resin was washed with CH_2Cl_2 and methanol and the filtrate was concentrated in vacuo to give dimer **2a** (8.1 mg). This yield was used to calculate a resin loading of 0.46 mmol g^{-1}.
Ester coupling procedure: Resin **8a** (295 mg) was swollen in CH_2Cl_2. A solution of allyl dimer **5** (133 mg, 0.41 mmol), DMAP (61 mg, 0.50 mmol), PTSA.H_2O (10 mg, 0.05 mmol) and DIC (110 μl, 0.70 mmol) in CH_2Cl_2 (3 ml) was added and the mixture was shaken for 5 hours. The resin was washed with CH_2Cl_2 and methanol to give **7b**. Deprotection and cleavage of resin **7b** as described above gave tetramer **2b** as a white solid, 79%.