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Solid-Phase Intermolecular Radical Reactions 2: Synthesis of *C*-Glycopeptide Mimetics via a Novel Acrylate Acceptor

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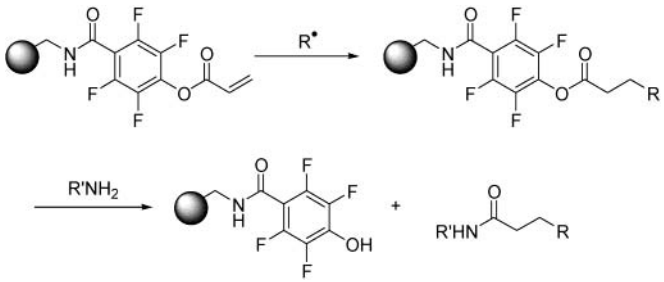
ABSTRACT



A novel tetrafluorophenol-linked acrylate is reported as an activated acceptor for intermolecular radical reactions. Addition of alkyl radicals led to pure products in good yields. We include here the first syntheses of C1- and C6-linked glycosides using a solid-phase radical methodology.

The field of solid-phase organic synthesis has recently seen the advent of a new class of reactions, namely, radical chain processes. The merits of free radical chemistry long evident in solution[1] are now being applied in conjunction with solid-phase technology to provide a wide range of both intermolecular[2−4] and intramolecular[5] solid-phase radical transformations. Our interests center on the particular advantages offered by intermolecular radical reactions. In the field of solution-phase radical chemistry, such transformations have traditionally relied upon chain conditions, thereby maintaining a low concentration of radicals. This position is tenable when the synthetically important bond-forming processes are faster than any other step in the chain process, and in the intramolecular mode, these conditions are usually met.

However, in the case of intermolecular radical reactions, more care needs to be taken to avoid unwanted side-reactions. This can often limit both the scope of transformations possible and the attainable yields. We have been keen to address these issues using a solid-phase methodology and reason that with an appropriately designed system, side-reactions occurring in solution will not compromise the yield or purity of the desired transformation on resin.

Following the success of our work on the addition of sulfonyl radicals to unactivated acceptors,[6] we have concentrated on the use of an activated acceptor for the addition of carbon-centered radicals. We were particularly interested in

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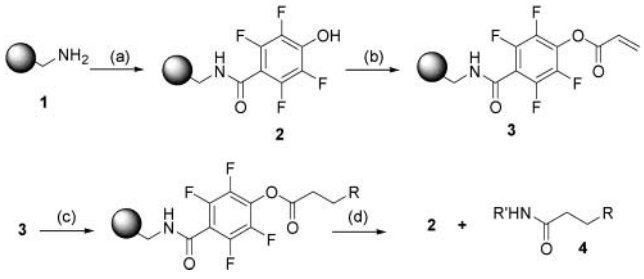
applying our methodology toward the synthesis of *C*-glycosides and *C*-glycopeptides. This field is currently expanding with a number of C-linked glycopeptide libraries appearing in the recent literature.[7−9] The choice of linker was governed by our desire to lessen the reactivity differential between primary, secondary, and tertiary carbon-centered radical additions while also developing a generic method for the synthesis of certain classes of C-linked glycopeptides. Others have shown how Wang acrylate can be utilized as an acceptor in radical additions.[3] However, it is interesting to note that these additions were not reported using tributyltin hydride and AIBN (although Enholm et al. have reported free-radical allyl transfers using allyl tributyltin on soluble non-cross-linked resins[4]). Others have reported difficulties when using the more conventional conditions with activated acceptors on solid supports.[10] There are also problems associated with using Wang acrylate when the addition does not proceed to completion since acrylic acid is not released cleanly from the resin under conditions required for product cleavage.

We decided to use the tetrafluorophenol linker **3** to address these problems for a variety of reasons. First, the acrylate acceptor is expected to have enhanced activity over a conventional acrylate ester due to the strong electron-withdrawing effects of the fluoro-aromatic moiety. Second, we anticipate that the release of products into solution by a range of nucleophiles would provide an extra point of product diversity and can be exploited in a combinatorial library as shown recently.[11] The corollary of this is that an array of saturated amides can be synthesized by radical addition and subsequent nucleophilic amine cleavage. Finally, since the cleavage reaction is responsible for introducing the product diversity essential for library generation, the radical addition need only be carried out upon a single acceptor, reducing the requirement for method development.

Since we began this work, synthesis of the tetrafluorophenol linker **2** has been reported[11] and some of our methodology has been adapted accordingly. Aminomethyl-polystyrene resin **1** was coupled to 2,3,5,6-tetrafluoro-4-hydroxy-benzoic acid under standard conditions as shown below (Scheme 1).

Scheme 1[a]



[a] Reaction conditions: (a) 3.5 equiv of 2,3,5,6-tetrafluoro-4-hydroxy-benzoic acid, 3.5 equiv of EDC, 7 equiv of DIPEA, DCM, 16 h; repeat using $^2/_3$ of the amount of (b) 5 equiv of acrylic acid, 5 equiv of DIC, 0.2 equiv of DMAP, DMF; (c) 5 equiv of RI, 5 equiv of Bu_3SnH, 1 equiv of AIBN, toluene, 100 °C, 1.5 h; (d) 3 equiv of R′NH_2, DCM, 16 h.

Loading for the phenol was assessed by acetylation (excess acetic anhydride/Et_3N, DCM, 16 h) and cleavage (4-methylbenzylamine, 2 equiv, DCM, 16 h); subsequent loadings and yields quoted are based on this calculation. Formation of acrylate ester **3** was carried out in DMF by sequential addition of acrylic acid, DMAP, and DIC.

We began by examining the addition of simple alkyl radicals to acceptor **3** (Scheme 1, Table 1).

Table 1

entry	R−X	R−NH_2	product	yield %[a]
1	*t*-butyl iodide	4-Me-BnNH_2	**4a**	98
2	*n*-butyl iodide	4-Me-BnNH_2	**4b**	79
3	isopropyl iodide	4-Me-BnNH_2	**4c**	99
4	cyclohexyl iodide	4-Me-BnNH_2	**4d**	78
5	phenethyl iodide	4-Me-BnNH_2	**4e**	68
6	cyclopentyl iodide	4-Me-BnNH_2	**4f**	68
7	**5**	4-Me-BnNH_2	**4g**[b]	53
8	**5**	PheOEt	**4h**[b]	44
9	**5**	TrpOMe	**4i**[b]	57
10	**5**	TyrOMe	**4j**[b]	21
11	**5**	SerOMe	**4k**[b]	16
12	**6**	PheOEt	**4l**[b]	37

[a] Isolated yields. [b] Column chromatography was required for analytical purity.

These reactions proceeded smoothly on resin with yields as quoted in Table 1 based on the loading of **3**. In the case of entries 1−6, product purification was limited to removal of excess amine either by washing the organic phase with 2 M HCl or filtration of the solution through an SCX solid-phase extraction cartridge. These results demonstrate the reactivity of acrylate acceptor **3** as well as the advantages of the solid-phase approach, with good to excellent yields reported for tertiary, secondary, and primary radicals (**4a**−**f**).[12]

The next stage of our research saw the application of this technology to the synthesis of C-linked glycosides. Radical addition of 6-iodo-1,2:3,4-*O*-diisopropylidene-α-l-fucopyranose **5** to acceptor **3** followed by cleavage with a selection of amines, including amino acid derivatives, afforded products **4g**−**l** in moderate yields as shown in Scheme 2 and Table 1 (entries 7−12).

The synthesis of C-linked glycosides via solid-phase radical methodology has not, to our knowledge, been

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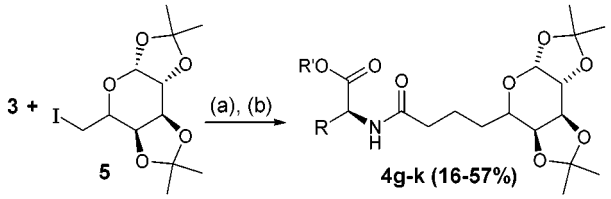
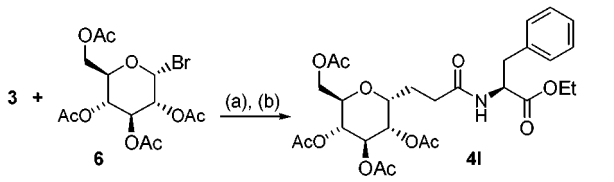
Scheme 2[a]



[a] Reaction conditions: (a) 5.0 equiv of **5**, 5.0 equiv of Bu_3SnH, 1.0 equiv of AIBN, PhMe, 100 °C, 2 h; (b) 2.0 equiv of RNH_2·HCl, 2.0 equiv of Et_3N, CH_2Cl_2, 16 h.

Scheme 3[a]



[a] Reaction conditions: (a) 5.0 equiv of **6**, 5.0 equiv of Bu_3SnH, 1.0 equiv of AIBN, toluene, 100 °C, 2 h; (b) 2.0 equiv of RNH_2·HCl, 2.0 equiv of Et_3N, CH_2Cl_2, 16 h.

previously reported, and despite the relatively low yields of entries 10 and 11, the examples outlined in Table 1 represent a novel means of accessing a range of interesting C-linked glycopeptide mimetics.

Radical chemistry has classically been used in the formation of C-linked glycosides at the anomeric center.[13] We were interested in extending our methodology to this important area.

The addition of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide to resin-bound acceptor **3** followed by cleavage with phenylalanine ethyl ester afforded the desired C-linked glycopeptide **4k** in 37% isolated yield (Scheme 3). Numerous attempts were made to improve the yields of entries 10−12. We believe that the low yields in these cases may be attributed to poor recovery of the reaction products from the resin. It may be the case that the high steric demand of the product does not easily allow free diffusion of the molecule out of the resin matrix.

In conclusion, we have developed a novel activated acrylate linker and successfully performed a range of intermolecular radical additions. Despite the low yields in some cases, this work represents, to our knowledge, the first successful synthesis of C-glycosides on a solid phase using a free-radical methodology. We have recently demonstrated that the analogous, solution-phase, pentafluorophenol esters are surprisingly stable species and may be isolated and characterized. We are therefore pursuing a complementary solution-phase approach to our methodology and also plan to extend the solid-phase approach to the synthesis of glycopeptide libraries.

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Supporting Information Available: Full characterization data for the cleaved products. This material is available free of charge via the Internet at http://pubs.acs.org.

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