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A novel route to functionalized PFP esters via rapid intermolecular radical addition to PFP acrylate mediated by ethylpiperidinium hypophosphite (EPHP)

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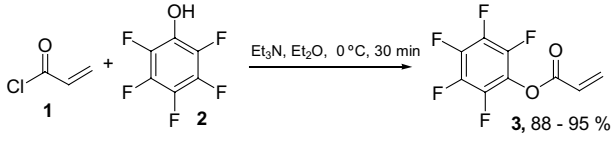
Abstract—Pentafluorophenyl (PFP) acrylate, a stable compact bifunctional scaffold undergoes rapid *N*-ethylpiperidinium hypophosphite (EPHP) mediated conjugate radical addition to yield a variety of active esters susceptible to further functionalization by aminolysis.

Intermolecular radical reactions provide an attractive means of carbon–carbon bond formation due to their mild conditions and functional group tolerance. However, while the functional group compatibility of these transformations is good, unwanted side reactions such as dimerization and polymerization, can severely limit the scope of the process. In recent years tri-*n*-butyltin hydride (TBTH), a toxic and expensive but highly effective chain carrier, has been employed by a number of groups to develop efficient radical mediated chain processes.[1] Although there have been numerous reports of alternative reagents to TBTH it is the case that no single reagent or protocol has been sufficiently general to replace this toxic reagent. In particular the difficulty in defining a reagent system that can be used for both inter- and intramolecular radical addition reactions has yet to be found.

We have previously established TBTH-mediated radical additions to an activated tetrafluorophenyl (TFP)-acrylate acceptor on solid support.[2] However, the success of that system we felt relied in part on the stability of the solid-supported substrates and products. We wished to develop a complimentary solution phase variant, but were uncertain whether a polyfluorinated acrylate or the resulting addition products would be sufficiently stable to make such an approach practical. Moreover we wanted to develop a tin-free methodology. We here report such a protocol employing pentafluorophenyl (PFP) acrylate **3**,[3] an air and moisture stable electron deficient olefin, which could easily be prepared in a single step and on large scale (0.1 mol) (Scheme 1).[4] It should be noted that this bifunctional acrylate could be stored for long periods of time (>2 years) at low temperatures (−20 °C) without a stabilizer.[5]

In a previous report we described a TBTH protocol for radical additions to PFP-sulfonate derivatives,[6] and we found that such reactions could be effected on the present PFP-acrylate species **3**. However we were keen to test a variety of non-tin alternatives.[7] We found the commercially available hypophosphite reagent EPHP



Scheme 1. Preparation of PFP acrylate.

Keywords: EPHP; Radical; Addition; Amides; PFP esters.
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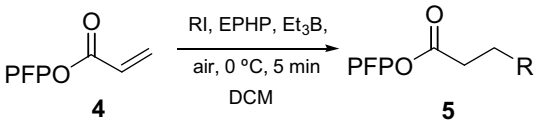
(1-ethylpiperidine hypophosphite 95% available from Aldrich, UK) to be the most suitable reagent for radical mediated C–C bond formation with PFP acrylate **3**.[8]

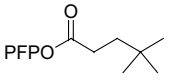
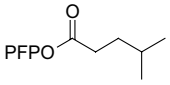
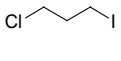
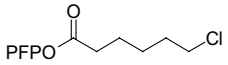
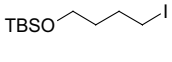
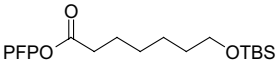
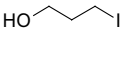
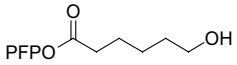
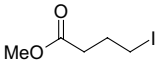
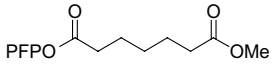
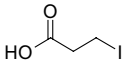
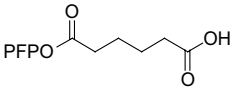
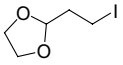
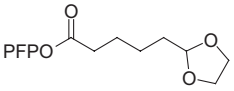
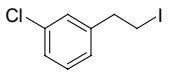
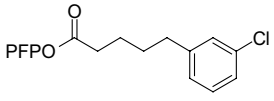
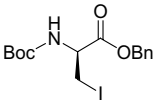
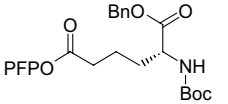
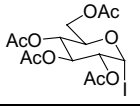
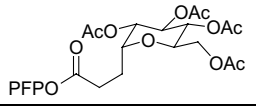
In the case of PFP acrylate, we found that to avoid decomposition,[9,10] 5 equiv of the chain carrier were required to effect intermolecular radical addition at 0 °C. The most suitable initiator for the chain process was a combination of triethylborane and oxygen, which can be employed at such temperatures. Abstraction of hydride from hypophosphite we envisaged would lead to a phosphorus centred radical, which could then abstract a halide atom in a similar manner to TBTH-mediated processes.[11] These reactions are particularly facile, involving short reaction times (<5 min) and efficient work-up procedure (ca. 95% of hypophosphite derived impurities can be removed by a simple aqueous work-up). In addition to this, no large excess of either iodide or acceptor is required (or indeed improves the yields), but rather they can be employed in a near 1:1 ratio, illustrating the efficiency of the transformation. Dichloromethane was chosen as the solvent for solubility reasons as well as to limit solvent–radical interactions.

Having established optimum reaction conditions we wished to demonstrate the effectiveness of this EPHP mediated radical addition to PFP acrylate **3** with a selected number of functionalized alkyl iodides (Table 1).[12] Yields are mostly good, although in some cases, such as alcohol **4e** (entry 5) and amino acid derivative **4j** (entry 10) lower yields were observed. In such cases the

Table 1. EPHP mediated functionalization of PFP



4 **5**

Entry	Iodide (**4a**–**k**)	Product (**5a**–**k**)	Isolated yield, %
1			85
2			78
3			78
4			57
5			41
6			72
7			67
8			68
9			66
10			39
11			80

halides were more susceptible to reduction and substantial quantities of the reduced products were observed (47% and 50%, respectively). Residual iodide (28%) was observed only in the case of TBS ether **2d** (entry 4). Most noteworthy is the very good yield achieved in the stereoselective formation of anomeric C-glycoside **5k** (entry 11).[13] Such acid-stable species, found in a variety of bio-active natural products, are most often prepared via free-radical methods.[14,15] In this case the anomeric radical undergoes stereocontrolled addition to the more electrophilic methylene of the acrylate **3**.[16] Such C-glycosidations are generally stereoselective due to the strong stereoelectronic influences that govern radical reactions at anomeric centres.[17] However, in the case of glucose derivatives, mixtures are often observed when TBTH is employed as the chain carrier and so the good yield and selectivity is noteworthy.[18] Also noteworthy is the good yield achieved for the carboxylic acid derivative **4g** (entry 7).[19]

Although these EPHP mediated additions work well with alkyl iodides, we have found that the analogous reactions with alkyl bromides usually proceed relatively poorly.[20] Similarly inefficient in our experience are reactions using electrophilic radicals generated from iodoacetamide and iodoacetonitrile.

Having established easy access to a large variety of alkyl PFP esters **5** the opportunity for further functionalization by the well-documented aminolysis of such species could be explored. PFP esters have been widely used in peptide chemistry since the 1970s, especially on solid support,[21] but have recently also found application in solution phase chemistry.[22] Their popularity is partly due to their stability and ease of handling. The use of the PFP group as an activating and protecting group is an advantage.[23] While unstable acid chlorides and carbodiimide reagents were important milestones in peptide chemistry, the need for harsh conditions and the potential racemization associated with such protocols has led to the development of a variety of active esters.[24]

From the many acidic phenols employed to prepare stable active esters, PFP derivatives have established a position as the peptide coupling method of choice due to predictable reactivity and efficiency of reactions. The ease of amine mediated nucleophilic displacement of the active ester is illustrated by the preparation of a small selection of amides from C-glycoside **5k** in excellent yields (Fig. 1).

In conclusion, we have established PFP acrylate **3** as a stable, bifunctional scaffold. Derivatization by means of fast and non-toxic EPHP-mediated conjugate radical additions of alkyl iodides yielded a variety of stable activated derivatives **5**, which can be functionalized further by aminolysis to yield amides in excellent yields. The surprising stability of the PFP-esters along with their ease of synthesis via this present methodology, along with their ability to undergo rapid amination makes the present methodology useful for the production of functionalized amide libraries.

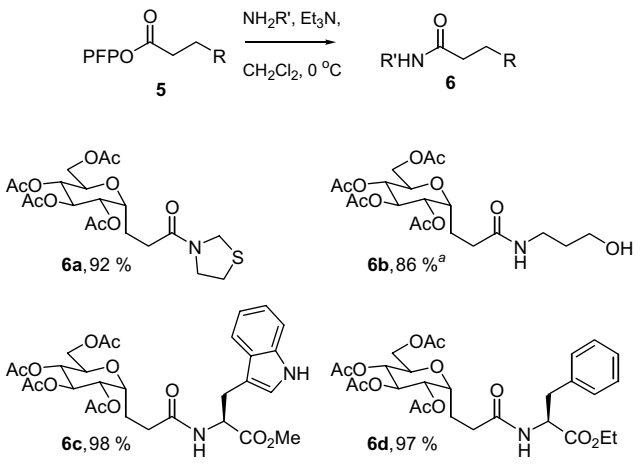


Figure 1. Examples of aminolysis products of **5k**.

Acknowledgements

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