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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8926–8929

Tributyltin hydride and 1-ethylpiperidine hypophosphite mediated intermolecular radical additions to 2,4,6-trichlorophenyl vinyl sulfonate

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Received 5 September 2007; revised 26 September 2007; accepted 4 October 2007
Available online 9 October 2007

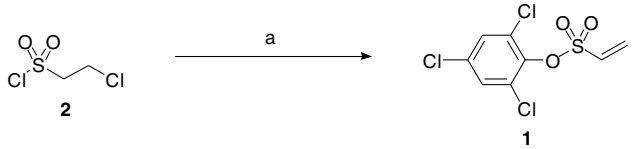
Abstract—2,4,6-Trichlorophenyl vinyl sulfonate smoothly undergoes intermolecular radical addition under mild initiation conditions mediated by tributyltin hydride and 1-ethylpiperidine hypophosphite (EPHP) to generate a range of functionalised alkyl sulfonamide precursors. This methodology can be used to prepare bifunctional pentafluorophenyl/2,4,6-trichlorophenyl sulfonates in good yields.

Sulfonamides are a common structural feature in a large range of important pharmaceuticals with a wide range of biological activities.[1] To date, the most commonly used synthetic method to make sulfonamides involves reaction of nucleophiles such as amines with sulfonyl chlorides.[2] Although this method is efficient the formation of the sulfonyl chloride is often not routine requiring harsh oxidising or strongly Lewis acidic conditions.[3] Previously, we have described the use of pentafluorophenyl (PFP) sulfonates as a shelf stable alternative to sulfonyl chlorides.[4,5] This functional group readily undergoes reaction with amines to generate sulfonamides and this can be achieved under aqueous conditions. For example, PFP vinyl sulfonate undergoes clean intermolecular radical addition using Bu_3SnH as the chain carrier to generate alkyl PFP sulfonates. Subsequent aminolysis has been used to derive a range of sulfonamides in good yields.[5]

Despite the utility of PFP-sulfonates we have spent considerable effort in finding alternatives, which address issues of cost and toxicity and we recently introduced 2,4,6-trichlorophenyl (TCP) sulfonates as a replacement for PFP-sulfonates.[6] As part of the development of the chemistry of TCP-sulfonates we now report radical additions to TCP vinyl sulfonate, an electron-deficient alkene, which is air and moisture stable. These radical additions are mediated by both Bu_3SnH and 1-ethylpiperidine hypophosphite (EPHP) and provide a simple and effective synthetic route to functionalised alkyl-TCP-sulfonates and a variety of sulfonamides that can be derived thereof.

Generation of the key TCP-vinyl sulfonate **1** was readily achieved. Addition of a solution of 2,4,6-trichlorophenol and triethylamine in dichloromethane to commercially available 2-chloroethane-1-sulfonyl chloride **2** at low temperature gave TCP-vinyl sulfonate **1** in good yield (Scheme 1).

Initially, we evaluated a range of conditions for the radical addition of simple radicals generated from iodides



2 **1**

Scheme 1. Reagents and conditions: (a) TCPOH, NEt_3, CH_2Cl_2, −10 °C, 82%.

Keywords: Radical addition; Tributyltin hydride; EPHP; TCP-sulfonate; Sulfonamide.
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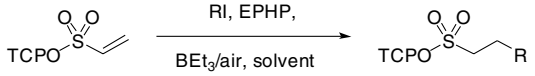
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.10.030

Table 1. Optimisation of EPHP mediated addition to TCP vinyl sulfonate



Entry	RI	EPHP (equiv)	Solvent	Temperature (°C)	Yield (%)
1	^{i}PrI	5	Dioxane	22	<5[a]
2	^{i}PrI	5	Dioxane	22	47
3	^{i}PrI	5	CH_2Cl_2	22	43
4	^{i}PrI	5	CH_2Cl_2	0	62
5	^{t}BuI	5	CH_2Cl_2	0	59
6	^{t}BuI	3	CH_2Cl_2	0	50
7	^{t}BuI	7.5	CH_2Cl_2	0	64
8	^{t}BuI	10	CH_2Cl_2	0	63

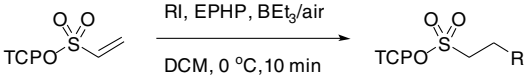
[a] BEt_3 omitted. Yield estimated by integration of the crude ^{1}H NMR.

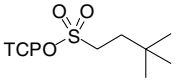
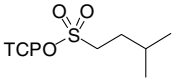
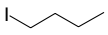
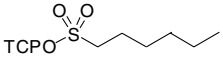
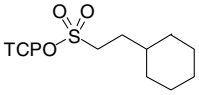
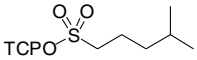
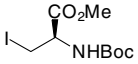
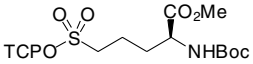
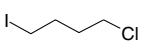
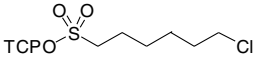
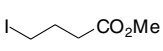
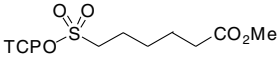
to TCP vinyl sulfonate (Table 1). We were particularly keen to utilise EPHP as a non-toxic alternative to Bu_3SnH as radical chain carrier in an analogous fashion to that reported previously.[7] Optimisation of the reaction conditions for the free radical addition of primary, secondary and tertiary radicals to TCP vinyl sulfonate indicated that higher concentrations of chain carrier gave higher yields (Table 1, entries 6–8) although the maximum yield was achieved at 7.5 equiv of EPHP (Table 1, entry 7). In addition, air alone did not initiate the free radical chain effectively (Table 1, entry 1) however triethylborane/air mixture at low temperature was found to proceed smoothly. This was best achieved via bubbling a volume of air through the reaction solution under a static inert atmosphere.

Our optimised EPHP conditions were then applied to a range of radical precursors and the efficiency of the addition evaluated (Table 2). These reactions were particularly facile requiring a reaction time of a few hours and the major side products, hypophosphite derived, could be removed with an aqueous work-up. It should be noted however that column chromatography was often required in the case of primary alkyl halides to remove ethyl radical addition by-products. The yields were generally moderate to good, although, with the primary alkyl halides, as expected, lower yields were observed. In the case of an amino acid derived iodide (Table 2, entry 6) significant amounts of the reduced iodide, vinyl sulfonate, ethyl radical addition and the product from elimination of HI were obtained even at low temperatures. In general it is notable that the reaction proceeds much better with alkyl iodides than with alkyl bromides.

Although the use of EPHP as a chain carrier in radical additions to TCP vinyl sulfonate was successful, problems with the efficiency of the reaction particularly with less readily generated radicals limited the scope of the methodology. In particular, we wanted a single set of reliable conditions which could be used to access rapidly a range of alkyl TCP sulfonates. In order to expand the generality of the reaction we returned to the more facile Bu_3SnH as the radical chain carrier under both AIBN and BEt_3/air initiation (Table 3).

Table 2. Substrate scope of EPHP–BEt_3/air mediated additions



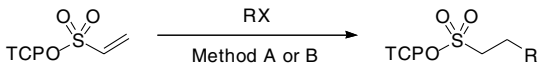
Entry	RI	Product	Yield (%)
1			64
2			62
3			51
4			72
5			33
6			<5[a]
7			27
8			<5[a]

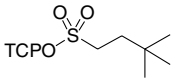
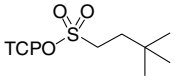
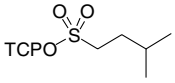
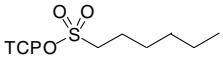
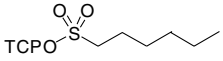
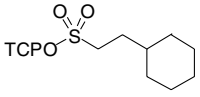
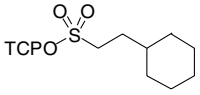
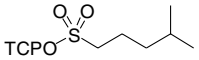
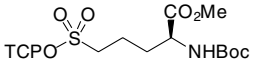
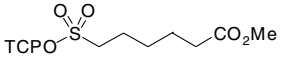
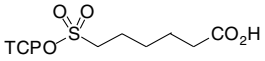
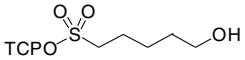
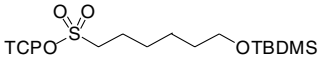
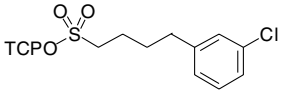
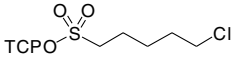
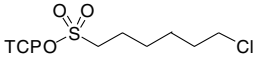
[a] Yield estimated by integration of the crude ^{1}H NMR.

Using Bu_3SnH as the chain carrier initiated with AIBN in refluxing toluene (Method A), we found that this intermolecular addition led to the corresponding alkyl sulfonate esters in moderate to good yields (Table 3). Initiation with BEt_3/air coupled with an improved purification protocol resulted in improved yields with simple alkyl sulfonates (Table 3, entries 1, 3, 4 and 6) and it was notable that secondary and tertiary bromides gave acceptable yields (Table 3, entries 2 and 7). We believe a significant proportion of this increase in yield was due to a more facile purification protocol involving column chromatography on KF or K_2CO_3 doped silica as described by Harrowven.[8]

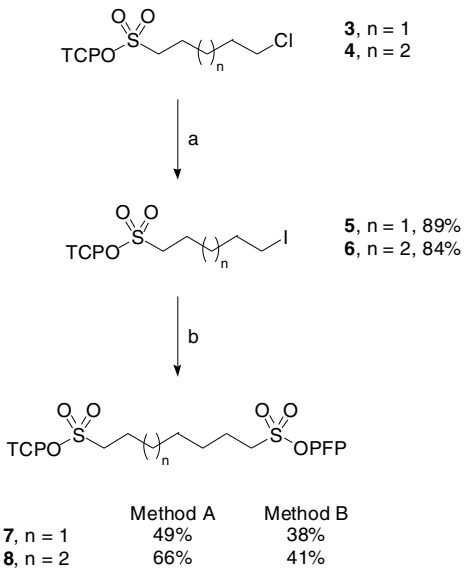
The functional group tolerance of this intermolecular radical addition route to TCP vinyl sulfonates is exemplified in reactions in the presence of esters, silyl ethers, aryl halides, acids, alcohols and other alkyl halides (Table 3). Also noteworthy is the addition of the radical generated from BocHN–A(I)–OMe, which was unsuccessful with EPHP as the chain carrier but was achieved, albeit in low yield, in the presence of Bu_3SnH (Table 3, entry 9). However, as before significant amounts of reduced halide and HI elimination products were isolated and in the case of BEt_3/air activation, the ethyl addition product. The relatively low yields in the case of the BEt_3/air activation with the more complicated substrates (Table 3, entries 9–16) can be attributed to

Table 3. Bu_3SnH mediated radical additions to TCP vinyl sulfonate



Entry	Product	Yield (%)	
		Method A[a]	Method B[b]
1		74	88
2		—	64
3		74	88
4		53	57
5		—	19
6		72	88
7		—	44
8		65	37
9		37	20
10		50	48
11		58	0
12		—	38
13		—	44
14		—	36
15		48	32
16		40	9

[a] 3 equiv RX, 0.05 equiv AIBN, 2.5 equiv Bu_3SnH, MePh, 110 °C, 2 h.
[b] 2 equiv RX, 3 equiv Bu_3SnH, 1 equiv BEt_3, air, CH_2Cl_2, 0 °C to rt, 18 h.



	Method A	Method B
7, n = 1	49%	38%
8, n = 2	66%	41%

Scheme 2. Reagents and conditions: (a) NaI, butanone, 120 °C (MW) 30 min; (b) Method A or B (see footnote Table 3).

a significant proportion of competing ethyl radical addition.

Encouraged by these results we also wished to prepare bifunctional alkyl TCP/alkyl PFP via a double radical addition protocol (Scheme 2). Conversion of **3** and **4** to iodides **5** and **6** was best achieved via microwave heating with NaI in butanone. The elevated temperatures accessed using microwave conditions resulted in complete reaction after 30 min compared to 18 h in refluxing acetone. Radical addition to PFP vinyl sulfonate using **5** and **6** gave the desired bifunctional TCP/PFP sulfonates **7** and **8** in moderate yields. As expected from our model studies an excess of Bu_3SnH was required and initiation with AIBN in refluxing toluene proved more effective, particularly in the case of **8**.

In conclusion, we have succeeded in carrying out intermolecular radical additions to TCP vinyl sulfonate using stannane mediated or stannane-free conditions to give alkyl sulfonates. Notably, we were able to carry out a double intermolecular radical addition to prepare bifunctional TCP/PFP sulfonates, which we envisage will be of significant utility as building blocks in two-directional synthesis.

Acknowledgements

We gratefully acknowledge the financial support of EPSRC, and BBSRC for support of our programme. We also gratefully acknowledge AstraZeneca, GlaxoSmithKline, Novartis and CEM Microwave Technology (UK). We gratefully acknowledge the EPSRC mass spectrometry service at Swansea for provision of mass spectra.

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2. For a recent example see: Deng, X. H.; Mani, N. S. *Green Chem.* **2006**, *8*, 835–838.
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