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LETTERS

Solid-Phase Intermolecular Radical Reactions 1. Sulfonyl Radical Addition to Isolated Alkenes and Alkynes

Stephen Caddick,* Daniel Hamza, Sjoerd N. Wadman

The Chemistry Laboratory, University of Sussex, Falmer, Brighton BN1 9QJ,
GlaxoWellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY

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Abstract: The addition of toluenesulfonyl radicals to solid-supported alkenes and alkynes gives bromo-sulfonyl alkenes and alkanes in good yields. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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Radical reactions have gained widespread and popular appeal in organic synthesis and are proven methods for the preparation of numerous classes of organic compounds.[1] In particular, cyclizations have provided many exciting and valuable methodologies for the construction of carbocyclic and heterocyclic rings and their application to natural product synthesis is a testament to their reliability and generality.[2] It is clearly the case that the synthetic potential of radical cyclization methods has been realised as a consequence of carrying out these reactions under chain conditions which maintain a low concentration of radicals. This position is ideal as long as the synthetically important bond-forming step(s) are faster than any of the other steps in the chain process. In the intramolecular mode, control of reaction conditions can help accommodate a range of rates for ring closure; this is not the case in the intermolecular mode because of the problems associated with competing combination processes. The use of a radical acceptor in excess or the adoption of non-chain radical conditions can often help to promote slow bimolecular radical reactions. However these tactics can give rise to complex mixtures and product isolation is often difficult. We suggest that the use of heterogeneous reaction conditions should aid isolation of products from such mixtures and therefore enable the use of non-chain protocols for bimolecular radical reactions.

We have decided to use solid-liquid heterogeneity to begin to address the problems of carrying out intermolecular radical reactions under non-chain conditions. For our particular programme, it became clear that we needed to examine the addition of a radical species to a solid-supported acceptor. There are a number of questions which need to be addressed, in particular those of resin compatibility and premature radical termination. However the successful use of polymer-supported tin reagents[3] (notably TBTH) and recent reports on intramolecular radical cyclisation[4] reactions indicated that such approaches may be possible. The purpose of this paper is to demonstrate, for the first time, that radical addition to unactivated solid-supported acceptors is a feasible and efficient process; this work paves the way for further investigations into intermolecular solid-phase radical reactions.[5]

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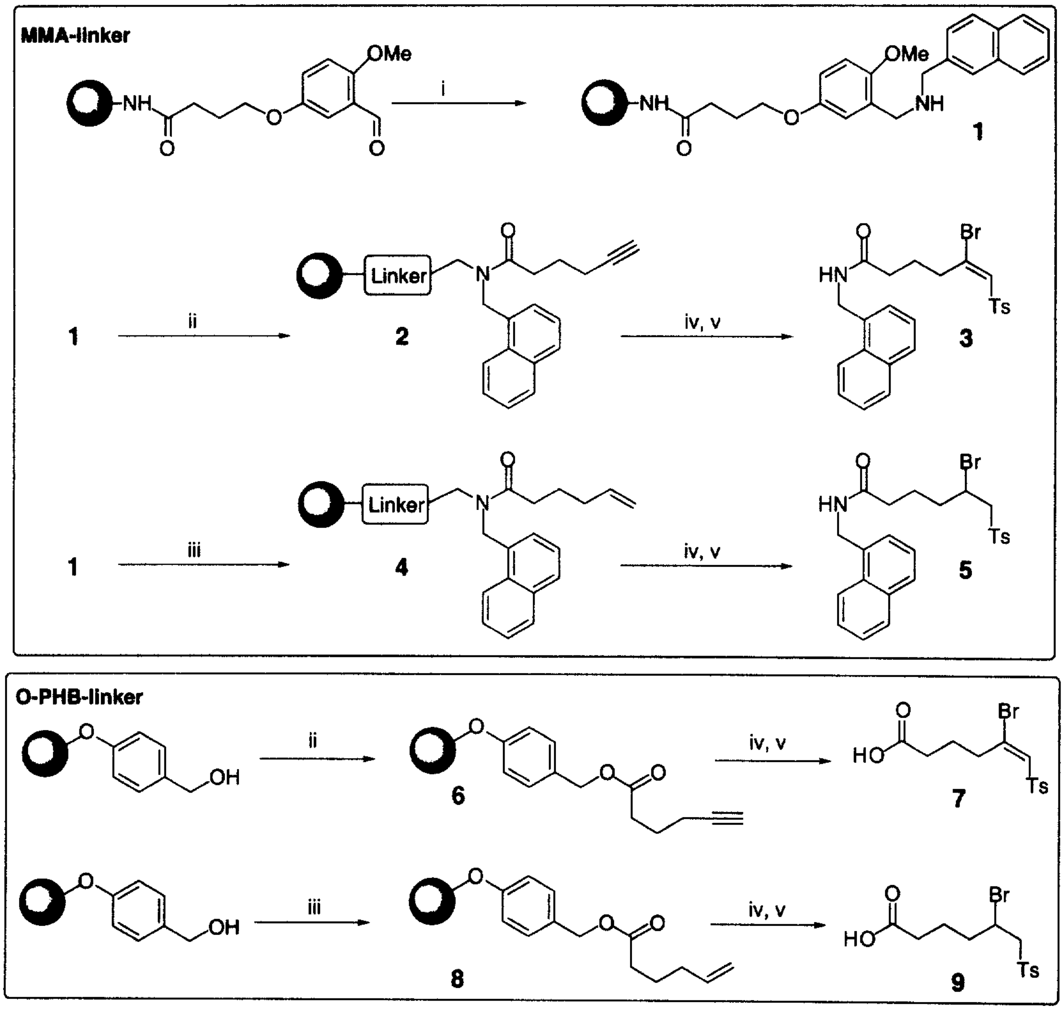
Our interest in the use of sulfonyl radical addition reactions[6] and the inherent synthetic versatility of products derived from such processes led us to investigate the addition of tosyl radicals to isolated alkenes or alkynes attached to a support. In order to carry out the work we used one of two linkers: monomethoxylaldehyde (MMA) or O-*p*-hydroxybenzyl (O-PHB). Addition of tosyl bromide to the substrates followed by cleavage using 95% TFA (aq) gave the products (**3**, **5**, **7**, **9**, scheme 1).

Scheme 1



Reagents and Conditions: i. $Me_4NBH(OAc)_3$ AcOH, DCM, 1-naphthalenemethylamine; ii. 5-Hexynoic acid, DIPEA, HATU, DMF; iii. 5-Hexenoic acid, DIPEA, HATU, DMF iv. TsBr, AIBN, toluene, 65 -70 °C; v. 95% TFA (aq).

The results of our work on the addition of tosyl bromide to alkyne and alkene substrates are given in table 1.[7] In general the reactions do not require inert reaction conditions and on a large-scale may be carried out in open vessels; however as can be seen from entries 1 & 2, the use of initiator is essential, providing good support for a radical process. It is striking that the reaction is sensitive to reaction solvent and linker; in some cases only decomposition is observed (entries 9, 10 & 13 - 18). However it is gratifying to note the excellent yield of addition to both alkenes and alkynes using a simple but high loading polystyrene-*O*-PHB resin (entries 7, 8).

Table 1: Addition of toluenesulfonyl bromide to supported alkenes and alkynes

Entry	Resin/loading(mmol/g)	Linker	Conditions	Product (%)*
1	PEG/0.41	MMA	Toluene, (no AIBN)	**3**, 0
2	PEG/0.41	MMA	Toluene, (no AIBN)	**5**, 0
3	PEG/0.26	MMA	Toluene	**3**, 25
4	PS/0.72	MMA	Toluene	**5**, 24
5	PS/0.72	*O*-PHB	Toluene	**7**, 57
6	PS/0.72	*O*-PHB	Toluene	**9**, 42
7	PS/0.72	*O*-PHB	Toluene	**7**, 94
8	PS/0.72	*O*-PHB	Toluene	**9**, 93
9	PS/0.72	*O*-PHB	MeCN	**7**, decomp
10	PS/0.72	*O*-PHB	MeCN	**9**, decomp
11	PS/0.72	*O*-PHB	Chloroform	**7**, 28
12	PS/0.72	*O*-PHB	Chloroform	**9**, 33
13	PEG/0.41	*O*-PHB	Cyclohexane	**7**, decomp
14	PEG/0.41	*O*-PHB	Cyclohexane	**9**, decomp
15	PEG/0.26	*O*-PHB	DMF	**7**, decomp
16	PS/0.72	*O*-PHB	DMF	**9**, decomp
17	PS/0.72	*O*-PHB	DMSO	**7**, decomp
18	PS/0.72	*O*-PHB	DMSO	**9**, decomp
19	PS/0.72	*O*-PHB	Dioxan	**7**, 45
20	PS/0.72	*O*-PHB	Dioxan	**9**, 33
21	PS/0.72	*O*-PHB	Ethyl acetate	**7**, 28
22	PS/0.72	*O*-PHB	Ethyl acetate	**9**, 37
23	PS/0.72	*O*-PHB	THF	**7**, 17
24	PS/0.72	*O*-PHB	THF	**9**, 19

*Yield refers to isolated product obtained after cleavage from resin (95% TFA (aq), 90 mins)

In conclusion we have found that the addition of toluenesulfonyl radicals to isolated alkenes and alkynes can be carried out under solid-phase conditions. It is particularly noteworthy that high-loading commercially available Wang-type resins can be used to deliver high yields of bromosulfonyl-alkenes and alkanes with obvious synthetic potential. However of perhaps greater significance is the finding that such reactions are highly efficient under conditions which do not necessarily proceed by a chain mechanism; this may be useful for developing resistant classes of intermolecular radical addition reactions. The ability of solid-phase technology to enhance the range of synthetically useful intermolecular radical reactions is an exciting prospect with numerous potential applications. The work presented in this paper demonstrates the feasibility of solid-phase bimolecular radical reactions and we believe that this general approach has considerable potential for organic synthesis.

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7 *General procedure for preparation of tosyl bromide:* To a stirred, aqueous solution (100ml) of sodium *p*-toluenesulfinate (1eq, 3g), bromine (1eq, 2.47g) was added dropwise with further stirring for 30 minutes upon complete addition. Crude TsBr was filtered and dried *in vacuo* (69% yield) and recrystallised from carbon tetrachloride (53% yield) m.p. 92-93° C. (Lit. 91-92° C).

General procedure for addition/cleavage: p-Toluenesulfonyl bromide (6eq, 0.6mmol) and azobisisobutyronitrile (6eq, 0.6mmol) were pre-dissolved in anhydrous toluene (~1ml) and added to a resin-linked acceptor (1eq, 0.1mmol). The reaction was performed in a 2ml Reactivial™ at 65-70°C for 16-22 hours and allowed to cool to room temperature. The resin was then washed copiously with portions of DMF, DCM, THF, DMSO, acetic acid and once with 20% DIPEA/DMF*. Cleavage from resin using 95% TFA(aq) gave the product. *Prolonged washing of the alkene addition products with base can lead to trace quantities of eliminated product.

Selected data for 7: ^{1}**H-NMR** (MeOD, 300MHz) δ: 7.86 (d, J^3= 8.0Hz, 2H, TsH2, TsH6), 7.49 (d, J^3= 8.0Hz, 2H, TsH3, TsH5), 7.11 (s, 1H, H6), 3.15 (t, J^3=7.5Hz, 2H, H4), 2.49 (s, 3H, CH_3-Ar), 2.34 (t, J^3=7.5Hz, 2H, H2), 1.87-1.94 (app. quintet, 2H, H3). ^{13}**C-NMR** (75MHz, d6-DMSO): 174.5, 145.8, 145.7, 138.5, 133.8, 131.1, 128.1, 36.0, 33.1, 24.1, 22.0. **HRMS:** (ESP) $[MNH_4]^+$ $C_{13}H_{19}BrNO_4S$ Required: 364.0218, found 364.0217. **MS** (ES+) $[M]^+$ 347, 345. **IR** υ_{max}/cm^{-1}(thin film): 3583, 3056, 2987, 2306, 1712, 1671, 1610, 1422, 1320, 1266, 1201, 1187, 1150, 1086, 738, 705.

Selected Data for 9: ^{1}**H-NMR** (MeOD) (300MHz) δ: 7.86 (d, J^3=8Hz, 2H, Ts H2 & H6), 7.50 (d, J^3=8Hz, 2H, Ts H3 & H5), 4.30-4.36 (m, 1H, H5), 3.85 (app. d, J^3=6.0Hz, 2H, H6+H6'), 2.50 (s, 3H, CH_3-Ar), 2.32 (m, 2H, H2), 2.08-2.16 (m, 1H, H4/H4'), 1.82-1.94 (m, 2H, H3/H3' + H4/H4'), 1.67-1.74 (m, 1H, H3/H3'). ^{13}**C NMR** (MeOD): 177.2, 147.2, 138.2, 131.6, 129.8, 64.7, 46.5, 39.0, 34.2, 24.0, 22.1. **HRMS** (ESP): $[MNH_4]^+$ $C_{13}H_{21}BrNO_4S$ Required: 366.0364, found 366.0374. **MS** (ES+) $[M]^+$ 349, 347. **IR** υ_{max}/cm^{-1}(thin film): 3583, 3055, 2987, 2306, 1713, 1610, 1422, 1320, 1266, 1150, 1087, 738, 706.