Pergamon

Tetrahedron Letters 39 (1998) 3651–3654

TETRAHEDRON
LETTERS

Reductive Cleavage of Resin Bound Arylsulfonates

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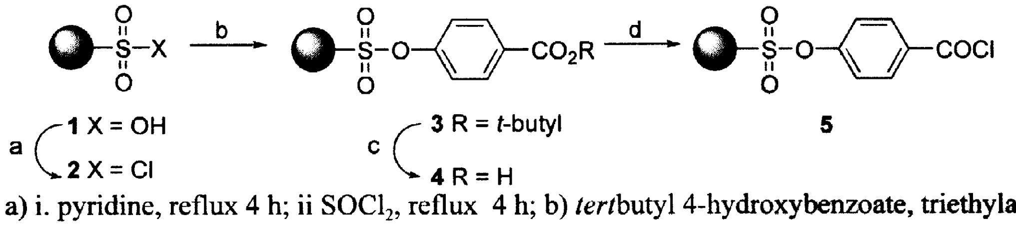
Received 4 February 1998; revised 11 March 1998; accepted 12 March 1998

Abstract: A 4-hydroxybenzoate was tethered to a solid support via an arylsulfonate bond. The carboxylate functionality was converted to a variety of esters and amides. The products were then liberated from the resin by Pd(0) catalyzed reductive cleavage of the arylsulfonate oxygen.

Keywords: Solid-Phase Synthesis, Sulfonic Acid and Derivatives, Reduction

The sulfonyl functional group plays a significant role in solution phase synthesis. However, sulfonyl functionality has seen only limited use in solid phase organic synthesis. Sulfonamide functionality has been shown to be potentially useful as solid phase linkers[1] particularly when employed in "safety catch" methodologies.[2-5] Recently a sulfonate linker was used for the synthesis of saccharide derivatives on solid support.[6] As part of a program to develop new solid phase synthetic methodology we became interested in exploring the use of arylsulfonates as solid phase linkers. Attachment of aryl rings to solid phase supports has been accomplished using phenolic hydroxy groups to Wang or Merrifield resins.[7] To compliment this methodology, we wished to develop a protocol which would allow the attachment of phenolic rings to the resin through formation of an aryl sulfonate bond. After appropriate chemical manipulation, the aryl functionality could be liberated from the resin by Pd(0) catalyzed reductive cleavage of the aryl-sulfonate oxygen bond. Other traceless linker strategies have utilized silicon and germanium linkages of the aryl ring to the resin and their removal from the resin under proteolytic cleavage conditions.[8,9] These strategies are particularly well suited for electron rich aromatic ring systems in which the proteolytic reaction proceeds rapidly. In contrast the reductive cleavage of arylsulfonates has been demonstrated to proceed effectively with electron poor aromatic rings in the solution phase.[10]

Scheme 1



a) i. pyridine, reflux 4 h; ii $SOCl_2$, reflux 4 h; b) *tert*butyl 4-hydroxybenzoate, triethylamine, CH_2Cl_2; c) TFA, CH_2Cl_2; d) $SOCl_2$, DCE.

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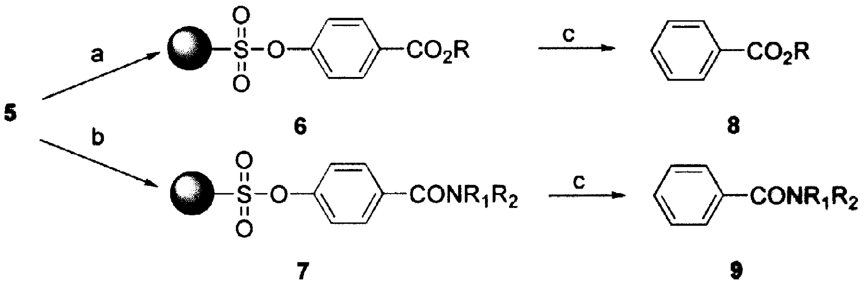
PII: S0040-4039(98)00640-6

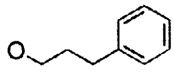
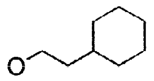
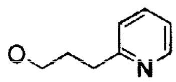
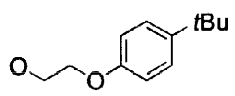
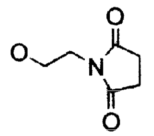
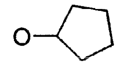
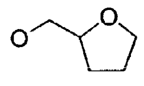
Sulfonyl chloride resin **2** was prepared from 2% cross-linked benzenesulfonic acid resin **1** (Dowex 50W ion-exchange resin) using a literature procedure.[11,12] The loading of this resin based on chlorine analysis was 4.3g/mmole. In the presence of triethylamine, *tert*-butyl 4-hydroxybenzoate was reacted with the sulfonyl chloride giving resin **3** (Scheme 1). The *tert*-butyl group in **3** was removed by treated with 15% of trifloroacetic acid in CH_2Cl_2 at room temperature. Chlorination of the resulting acid **4** with thionyl chloride in dichloroethane at reflux for 12 h afforded the benzoyl chloride sulfonate resin **5**. Elemental analysis of **5** for Cl confirmed the reaction occurred cleanly and in nearly quantitative yield. Reaction of **5** with 3 molar equivalents of various alcohols in the presence of 1.5 molar equivalents of triethylamine in CH_2Cl_2 generated a series of solid-supported benzoate esters **6** which were confirmed by elemental analysis and the presence of a carbonyl absorption in the IR spectrum in the range of 1702-1742 cm^{-1} (Scheme 2). Similarly resin bound benzamides **7** could be prepared by reacting a 3 fold excess of various amines with resin bound acid chloride **5**. After some experimentation it was found that benzoate esters **8** (Table 1) and benzamides **9** (Table 2) could be cleaved from the resin by palladium mediated reduction of the aryl-sulfonate oxygen bond at 110-140°C using triethylamine and formic acid in DMF. The cleavage products were isolated in useful yields as outlined in Tables 1 and 2.[13]

Scheme 2



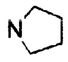
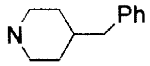
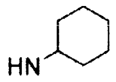
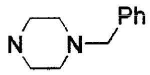
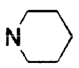
a) ROH, triethylamine, DCE; b) HNR_1R_2, triethylamine, DCE; c) triethylamine, formic acid, Pd(OAc)$_2$, DPPP, 110-140°C.

Table 1 Yields of Benzoate Esters.

Compound	OR	Overall Yield (%)	Compound	OR	Overall Yield (%)
8a[14]		74[a]	**8e**[14]		85[b]
8b		40[a]	**8f**		52[b]
8c		52[a]	**8g**		63[b]
8d[14]		45[a]	**8h**[14]		36[a]

Cleavage conditions: **a**. 8 equiv. TEA, 7.5 equiv. of FA, each 0.2 equiv. of Pd(OAc)$_2$ and DPPP, heating at 110 °C for 12 h. **b**. The amount of TEA & FA is same as condition **a** except 0.5 equiv. of Pd(OAc)$_2$ and DPPP under hearting at 140 °C for 12 h.

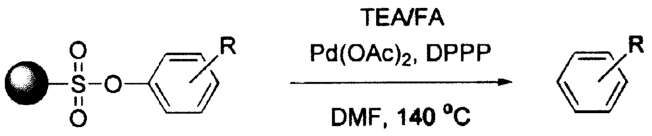
Table 2 Yields of Benzamides

Compound	NR_1R_2	Overall Yield (%)	Compound	NR_1R_2	Overall Yield (%)
9a[14]		18	**9e**[14]		26
9b[14]		35	**9f**		15
9c[14]		28	**9g**[14]		13
9d[14]		37	**9h**[14]		45

Cleavage conditions: 8 equiv. TEA, 7.5 equiv. of FA, each 0.2 equiv. of $Pd(OAc)_2$ and DPPP, heating at 140 °C for 12 h.

The yields in Tables 1 and 2 were calculated based on the loading of resin **2** and thus represent the yield of the overall process. In general it was found that esters could be cleaved at lower temperatures (110°C) and in somewhat better yields than the amides which required a higher temperature (140°C) for the cleavage reaction to occur. The lower yields observed in the cleavage of the benzamides was thought, at least in part, to be due to the reduced electron withdrawing effect of amides compared to the esters.

Table 3 Effect of Functional Group on Aromatic Ring Cleavage



Entry	R	Position	Overall Yield (%)
1	COPh	*para*	68
2	COOEt	*meta*	24
3	CH_2COOEt	*para*	5
4	OEt	*para*	0

To explore this possibility cleavage of a number of aryl ring systems from the sulfonate support was examined. These results are summarized in Table 3. When R is both an electron withdrawing group and is located in the *para* position, the cleavage reaction gave the best yield of liberated product (entry 1). The solid-supported aromatic ring with a neutral or electron donating group in *para* position to the sulfonate linkage afforded little if any compound detached from the resin (entries 3 and 4). Ethyl benzoate was obtained in 24% yield when the ethyl carboxylate group was present in *meta* position of resin bound benzene (entry 2). Thus the electron withdrawing groups *para* to sulfonate oxygen appear to be important for efficient cleavage reaction using this sulfonate resin.

In summary, the use of arylsulfonates as solid phase supports has been demonstrated. Readily available sulfonyl chloride resin can be reacted with a variety of phenols to produce resin linked arylsulfonates and ester and amide forming reactions have been carried out on the resin. Cleavage reaction conditions have been developed which produce products having an aryl C-H bond at the point of resin attachment. This chemistry works best when an electron withdrawing functionality is present *para* to the sulfonate oxygen. Further studies of this conceptionally novel traceless linker strategy with other sulfonate resins which may be more amenable to wide a variety of solid phase synthetic transformations and cleavage reactions are ongoing in our laboratories.

Acknowledgement

The authors would like to thank Dr. Jack Hodges and Dr. Robert Kennedy for helpful discussions during this work.

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