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LETTERS

Synthesis of alkyl sulfonates from sulfonic acids or sodium sulfonates using solid-phase bound reagents

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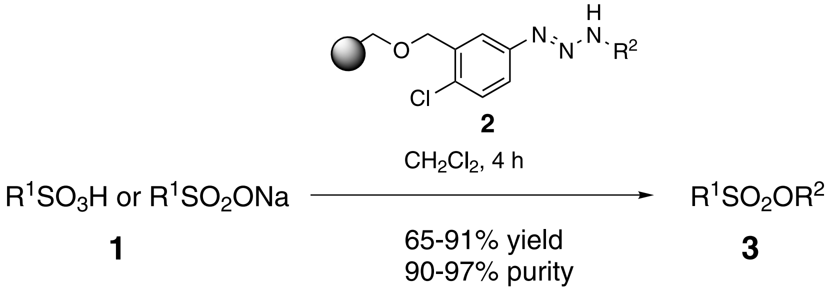
Abstract—An efficient and selective method for the synthesis of sulfonic esters from sulfonic acids or sodium sulfonates using polymer-bound primary triazenes based upon the T2* linker has been developed. The purities of the esters obtained are usually greater than 95% without any further purification steps. © 2001 Elsevier Science Ltd. All rights reserved.

Sulfonic esters are important intermediates in organic synthesis and are suitable precursors for sulfonamides and act as alkylating reagents. In addition, various sulfonic esters inhibit interesting pharmacological properties.[1]

The reaction of sulfonyl chlorides with alcohols in the presence of a base provides a well-established access for alkyl sulfonates.[2,3] However, the capability of a β-elimination to form sulfenes is a serious drawback. Other methods include the reaction of sulfonic acids with orthoformates[4] and other electrophiles such as epoxides[5] or aziridines.[6]

In general, sulfonic esters are prepared under mild conditions from the corresponding sulfonic acids by reaction with diazoalkanes.[7,8] Although synthetically useful, the drawback of this method is the lack of general accessibility of suitable diazoalkanes. In addition, the parent compound for this transformation, diazomethane, and its higher homologues are considered highly toxic and explosive.[9] Similarly, the well-known precursors for diazomethane (such as Diazald®) are also irritant.[10]

Recently, we have demonstrated the use of triazenes as linker moieties in solid-phase organic synthesis to detach amines,[11] ureas,[12] amides,[12] and guanidines.[13] In addition, we[14–16] and later others[17] have demonstrated that immobilized primary triazenes derived from an aromatic diazonium ion and a primary amine are suitable for the alkylation of esters and for the synthesis of alkyl halides. In this case, the triazene moiety serves as a capped diazoalkane equivalent delivering the alkyl group upon protonation. To the best of our knowledge, the reaction of sulfonic acids with triazenes to give alkyl sulfonates has not been reported before.



Scheme 1. Synthesis of sulfonic esters.

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Table 1. Preparation of sulfonic esters **3**

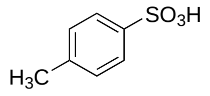
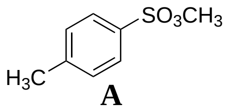
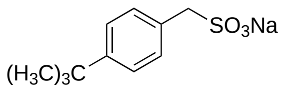
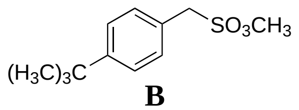
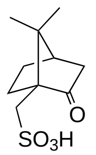
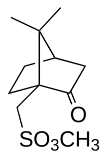
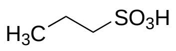
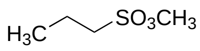
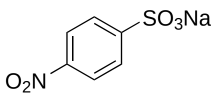
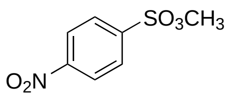
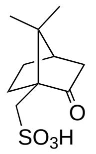
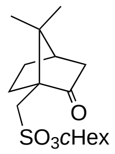
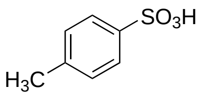
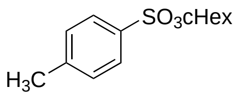
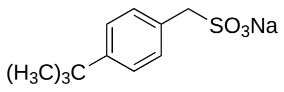
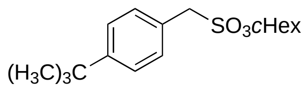
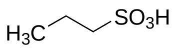
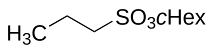
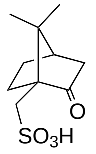
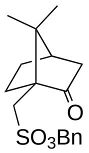
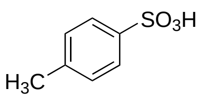
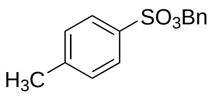
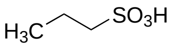
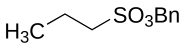
Sulfonic acid/sulfonate	R^1 resin **2**	Product **3** conditions[a]	Yield [%] (purity [%])
	Me	 **A**	86 (97[b])
	Me	 **B**	90 (97[b])
	Me	 **A**	89 (96[b])
	Me	 **B**	77 (95[b])
	Me	 **B**	88 (98[c,d])
	*c*Hex	 **A**	87 (>95[e])
	*c*Hex	 **A**	91 (>95[e])
	*c*Hex	 **B**	81 (>95[e])
	*c*Hex	 **A**	77 (95[b])
	Bn	 **A**	66 (>95[e])

Table 1. (*Continued*)

Sulfonic acid/sulfonate	R^1 resin **2**	Product **3** conditions[a]	Yield [%] (purity [%])
	Bn	 **A**	84 (>90[e])
	Bn	 **A**	65 (>90[e])

[a] **A**: 0.1 mmol sulfonic acid, 0.5 g resin **2**, CH_2Cl_2, 4 h; filtration. **B**: 0.1 mmol sulfonate, 0.5 g resin **2**, 0.1–0.25 g Lewatit SP 120 H form, CH_2Cl_2, 4 h; filtration.

[b] Determined by GC.

[c] Determined by HPLC.

[d] A mixture of 90:10 of *para*- and *ortho*-substituted both starting material and product.

[e] Determined by ^1H NMR spectroscopy. *c*Hex = cyclohexyl.

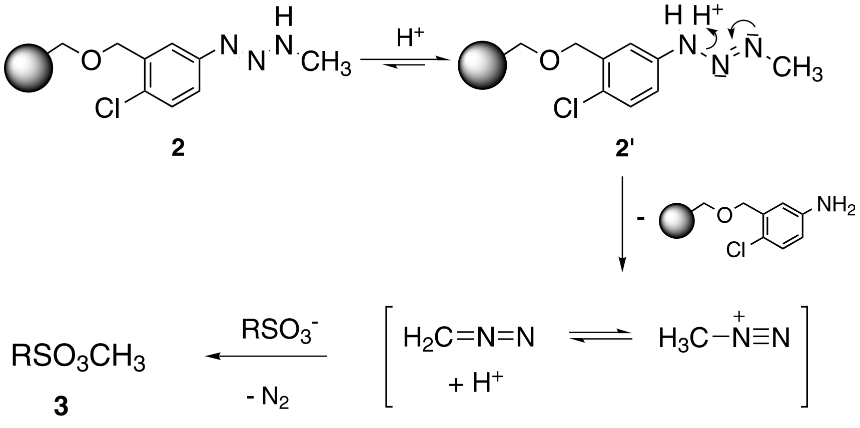
Therefore, the use of triazenes in the synthesis of sulfonic esters was examined. In this case, the triazenes of type **2** were used, which were synthesized from the bench-stable polymer-bound diazonium salt T2* by reaction with various amines to give the triazenes **2** in excellent yields.[18] Treatment of the triazenes **2** as a suspension with 0.3 equivalents of the corresponding sulfonic acid **1** in dichloromethane at room temperature for 4 h, filtration, and evaporation of the solvent gave rise to the sulfonic esters **3** (Table 1).

Similarly, sodium sulfonates **1** can be used as starting materials when the synthesis was conducted in the presence of an acidic ion-exchange resin (Lewatit SP 120 H form). In this case, the ion-exchange resin protonates the sulfonate to give the active sulfonic acid and also retains the sodium ion (Scheme 1).

Using this method, twelve different sulfonates were prepared in excellent yield and purities, which were determined by GC, NMR and/or HPLC methods. The method is applicable to primary and secondary esters. Aromatic, branched and alkyl sulfonic acids are suitable (Table 1).

Since a large variety of primary amines can potentially be coupled to the T2* resin, this method is suitable for various scaffolds.

Although alkylation or acylation of primary triazenes proceeds cleanly only at the aliphatic end of the triazene moiety (according to resonance structure **2**), protonation delivers the aliphatic diazonium ion (presumably via resonance structure **2′**), which rapidly reacts with the sulfonate to furnish the corresponding ester (Scheme 2). This has already been demonstrated in the reaction of triazenes and diazoalkanes with nucleophiles. At this point it should be noted that phenethyl amine is not transferable due to a β-elimination of the phenethyl diazonium ion resulting in the formation of styrene. Benzyldiazonium ions are, in contrast to methyldiazonium ions, calculated to be highly unstable or even non-existent.[19]



Scheme 2. Proposed mechanism of sulfonic ester formation.

In conclusion, a novel technique for the synthesis of alkyl sulfonates has been developed giving rise to the title compounds in high yield and purity.

Acknowledgements

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