SHORT PAPER

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Clean-chemistry sulfonation of aromatics[†]

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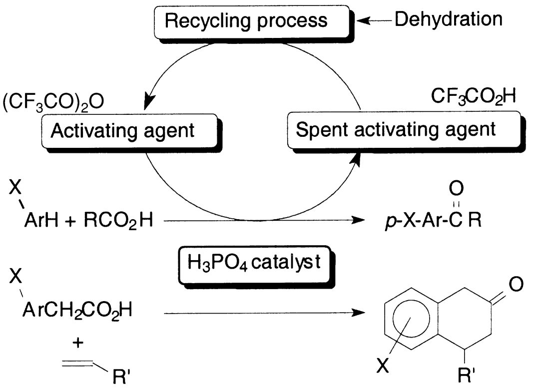
A solution of TFAA/H_2SO_4 is an atom-efficient liquid-phase system for rapid sulfonation of aromatic structures; H_2SO_4 is consumed stoichiometrically and the spent trifluoroacetic anhydride (TFAA) is readily recovered as trifluoroacetic acid (TFA) which can be recycled to TFAA.

Keywords: sulfonation of aromatics, clean chemistry

Sulfonation of aromatics is an important industrial process used for both bulk and small-scale production.[1] Like other aromatic conversions – nitration, alkylation and acylation – sulfonation presents a particular, and pressing, challenge in terms of developing a clean-chemistry process.[2] We have reported on a clean-chemistry method of aromatic acylation using a carboxylic acid with trifluoroacetic anhydride (TFAA) as a recyclable activating agent and with H_3PO_4 as catalyst (Scheme 1).[3] This system was used to prepare a precursor structure in the synthesis of tamoxifen and recently we extended its application to the preparation of 2-tetralones starting directly with a (substituted) phenylacetic acid and an alkene (Scheme 1).[4]



High yields with X = MeO and H_3PO_4 (0.1-0.2 equiv)

Scheme 1

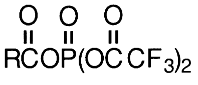
We elucidated the role of H_3PO_4 as a covalent catalyst: our mechanistic work (including ^{31}P and ^{19}F NMR observations) substantiated the role of **1**, an acyl bis-(trifluoroacetyl)phosphate, as the most active acylating agent in the reaction cycle.[3a, 5]

Use of H_2SO_4 instead of H_3PO_4 in our study of aromatic acylation led to sulfonation as well as acylation. This indicated that an active sulfonating agent, such as trifluoroacetylsulfuric acid (**2**) or bis(trifluoroacetyl)sulfate (**3**), was formed in the reaction system; production of these by reaction of TFA and SO_3 has been reported in a study of sulfonation of alkenes.[6] Formation of acetylsulfuric acid, and bisacetylsulfate on reaction of H_2SO_4 with Ac_2O is well established[7] and is patented as a sulfonation process.[8] However, accumulation of sulfoacetic acid[7] (**4**) is a drawback here as is the use of a chlorinated hydrocarbon solvent.

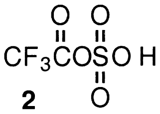
We report here an evaluation of TFAA/H_2SO_4 as an aromatic sulfonation system with emphasis on product yield, recovery of the spent TFAA (as TFA), consumption of H_2SO_4 and eliminating use of a co-solvent.

Addition of TFAA (2.1 equiv) to conc. H_2SO_4 (1 equiv) led to a homogeneous solution on stirring for approximately 3 h.[9] The aromatic substrate (1 equiv) was added directly to this solution. (Reaction progress was monitored by adding one drop of the neat solution to D_2O and recording the ^1H NMR spectrum.) Addition of the required stoichiometric amount of water, followed by removal of TFA by distillation, yielded the crude sulfonic acids. HPLC analysis was used to confirm product identity and to establish isomer ratios. The results are given in Table 1. Chlorobenzene and 4-nitrotoluene were readily sulfonated. However, nitrobenzene could not be fully sulfonated even over an extended reaction period. The aromatic substrates all dissolved in TFAA/H_2SO_4 except naphthalene. Nonetheless, quantitative conversion to sulfonated products was observed when this was used as a fine powder. Both mono- and di-sulfonation occurred: at low temperature the kinetically formed product (naphthalene-1-sulfonic acid) predominated (Table). With two equivalents of the sulfonating agent naphthalene-1,5-disulfonic acid was formed in 79 and 97% yield at 0 and –50°C respectively, with the balance occurring as naphthalene-1-sulfonic acid.

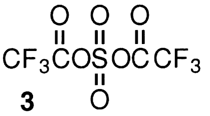
In summary, we have shown that a homogenous mixture of TFAA/H_2SO_4 is an atom-efficient system for facile sulfonation of aromatics. This system may have application to large-scale, as well as small-scale, reactions.


$R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{P}}(O\overset{O}{\overset{\|}{C}}CF_3)_2$

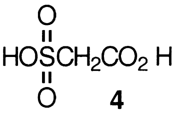
1


$CF_3\overset{O}{\overset{\|}{C}}O\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O\,H$

2


$CF_3\overset{O}{\overset{\|}{C}}O\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O\overset{O}{\overset{\|}{C}}CF_3$

3


$HO\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}CH_2CO_2\,H$

4

Structures 1-4

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 General results for aromatic sulfonation in TFAA/H_2SO_4

Ar–H	Ar–SO_3H yield/%; isomer/%	T/°C	*t*/min
Benzene	100	10	10
Toluene	100; *o/p:* 2.4/97.6	10	10
Chlorobenzene	100; *o/p:* 5.4/94.6	10	10
p-Xylene	100	10	10
Naphthalene	100; 1/2/1,5-di: 56.5/5.8/37.7	10	10
Naphthalene	100; 1/2/1,5-di: 70.3/10.3/19.4	-50	10
4-Nitrotoluene	100; 2-sulfonic acid	60	30
Nitrobenzene	50; *m*	60	72 h

Experimental

HPLC analyses were carried out using a Zorbax Eclipse XDB-C8 column, 4.6 mm × 250 mm or a Phenomex Nucleosil 10SB column, 4.6 mm × 250 mm, with a photodiode array detector (observation wavelengths 238–280 nm). A mobile phase of 40% EtOH/H_2O v/v, pH 3.0, 0.1 M citric acid and 0.15 M sodium perchlorate was used with a flow rate of 1 ml/min. Authentic samples (Sigma) were used as reference materials.

General sulfonation procedure: TFAA (30 ml, 0.21 mol) was added to conc H_2SO_4 (10 g, 0.1 mol) with cooling (ice water) in a dry atmosphere and stirred for 3h after which time complete dissolution of H_2SO_4 was achieved; the solution appeared light brown. The aromatic substrate (0.1 mol) was added dropwise to the cooled solution (ice-water) and this solution was stirred for 10 min (or heated to reflux in the case of 4-nitrotoluene and nitrobenzene); a precipitate formed at this stage. Water (4.5 ml, 0.25 mol) was added dropwise with cooling (ice-water). TFA (28.5 ml, 0.37 mol) was removed by distillation to leave the crude aryl sulfonic acid. For HPLC analysis a small reaction sample was taken prior to distillation and the TFA was removed using a vigorous flow of nitrogen.

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9 This process is exothermic as is the subsequent aromatic sulfonation. We restricted our work to small-scale reactions and did not examine the reaction calorimetry of the individual steps.