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Rapid and efficient chemoselective and multiple sulfations of phenols using sulfuryl imidazolium salts

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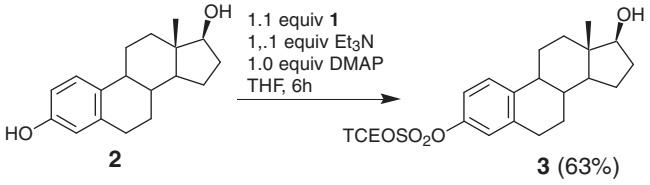
ABSTRACT

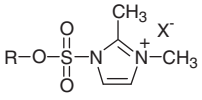
Phenolic sulfates protected with a trichloroethyl or trifluoroethyl group were rapidly and efficiently obtained by reacting phenols with sulfuryl imidazolium salts in the presence of DBU. Phenolic hydroxyl groups could be sulfated in good yield in the presence of aliphatic hydroxyl groups and multiple sulfations were also readily achieved.

Sulfation is an important tactic by which nature mediates the activity of biomolecules, such as carbohydrates and nucleosides as well as phenolic derivatives, such as steroids, flavonoids, and tyrosine residues within proteins.[1–6] Sulfation is also a major detoxication mechanism for endogenous compounds and xenobiotics containing phenolic and aliphatic hydroxyl groups.[7] It has recently been shown that highly sulfated polyphenols exhibit interesting biological properties and are being examined as mimics of glycosaminoglycans such as heparin.[8] Sulfated phenols have traditionally been prepared by treating the substrate with a sulfating agent, such as a sulfur trioxide–amine or amide complex, sulfuric acid or sulfuric acid/DCC.[9] Despite the success of this approach it does have some limitations. Since the sulfated products are highly polar and not highly soluble in most organic solvents, they are not amenable to further transformations and so the sulfation step must be carried out at or near the end of the synthesis. In the case of multiple sulfations, as each sulfate group is introduced the nucleophilicity of the remaining hydroxyl groups is reduced. Moreover, charge repulsion between adjacent sulfate groups further affects reactivity. Hence, a distribution of products is commonly observed making the purification of the highly polar products very tedious and time consuming.[9] As a result of these issues more recent efforts have focused on installing the sulfate group(s) as a protected sulfodiester(s).[9] The advantage of this approach is that the protected neutral sulfates can be purified by conventional methods, easily characterized and, if necessary, the product can be subjected to further transformations and then deprotected under mild conditions.

Several years ago we reported that the trichloroethyl (TCE) group is an effective protecting group for aryl sulfates. It is introduced using $Cl_3CCH_2OSO_2Cl$ (**1**) in the presence of Et_3N and DMAP in dry THF and removed using Pd/C or Zn in the presence of ammonium formate.[10] This methodology has now been widely used in the preparation of aryl sulfates.[11] Although reagent **1** gives the desired protected arylsulfates in good yield, in some instances we found that the results were less than optimal. For example, sulfa-



Scheme 1. Sulfation of estradiol at O-3 using reagent **1**.



4, R = TCE, X = TfO^-
5, R = TFE, X = TfO^-

Figure 1. Structures of sulfuryl imidazolium salts **4** and **5**.

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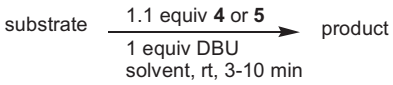
Table 1
Monosulfation of phenols using reagents **4** and **5** and DBU[a]



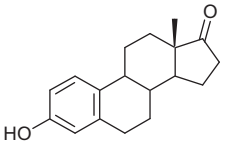
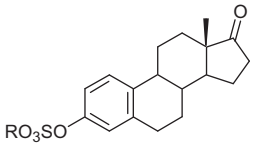
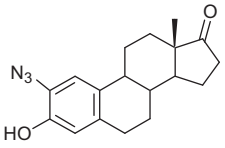
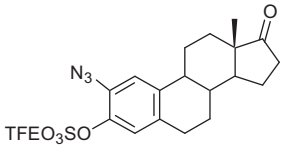
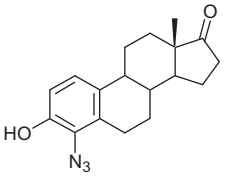
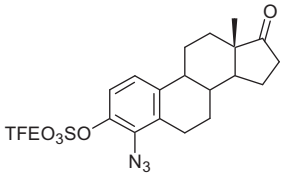
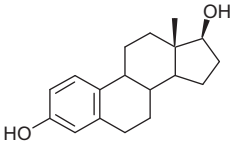
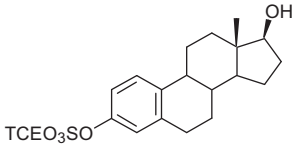
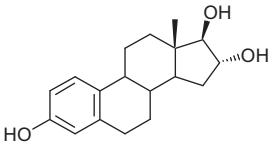
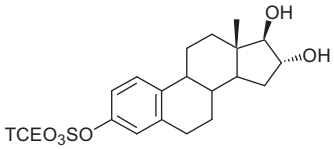
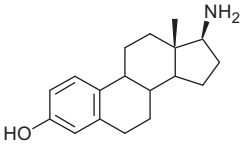
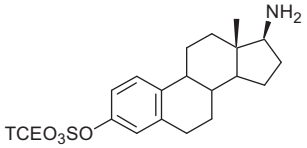
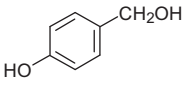
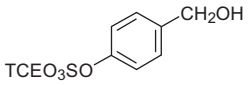
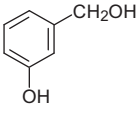
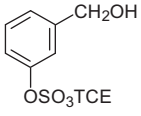
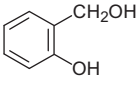
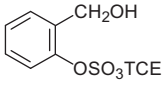
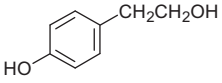
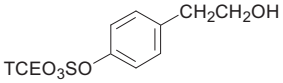
Entry	Substrate	Sulfating agent	Product	% Yield
1	 **6**	**4**	 **8**, R = TCE	96 (**8**)
2		**5**	**9**, R = TFE	98 (**9**)
3	 **10**	**5**	 **11**	89
4	 **12**	**5**	 **13**	86
5	 **2**	**4**	 **3**	90
6	 **14**	**4**	 **15**	88[b]
7	 **16**	**4**	 **17**	80
8	 **18**	**4**	 **19**	84
9	 **20**	**4**	 **21**	84
10	 **22**	**4**	 **23**	0

Table 1 (*continued*)

Entry	Substrate	Sulfating agent	Product	% Yield
11	 **24**	**4**	 **25**	83

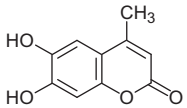
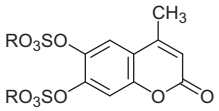
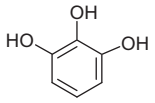
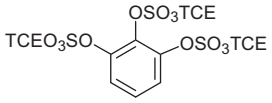
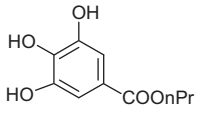
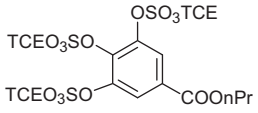
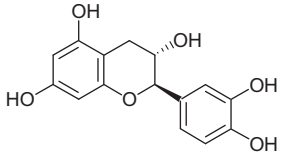
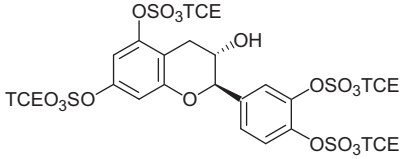
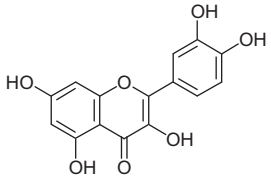
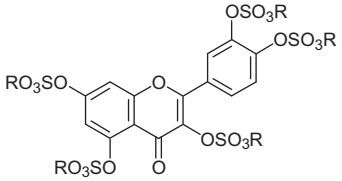
[a] All reactions were conducted in CH_2Cl_2 unless stated otherwise.
[b] Conducted in DMF–CH_2Cl_2.

tion of the phenolic OH of estradiol (**2**, Scheme 1) using reagent **1** for 24 h gave a mixture of mono- and disulfated products and, after a tedious purification the desired compound **3** was isolated in only modest yield. Therefore, we began to look for alternative approaches or reagents for performing this transformation.

We recently developed sulfuryl imidazolium salts, such as compounds **4** and **5**, for introducing TCE and trifluoroethyl (TFE) -protected sulfates into compounds having aliphatic hydroxyls such as carbohydrates (Fig. 1).[12–14] The TFE group is removed using *t*-BuOK in refluxing *t*-BuOH[15,16] or with NaN_3 in warm DMF.[14] Our success with using these reagents for sulfating alkyl hydroxyls prompted us to examine these reagents for preparing aryl sulfates. Here we report that protected aryl sulfates can be prepared in excellent yields using sulfuryl imidazolium salts **4** and **5** and DBU. Sulfations, including multiple sulfations of polyphenols, that previously took hours using reagents such as **1** can now be accomplished in high yield within minutes and sulfation of phenolic hydroxyls in the presence of other nucleophilic residues can be now be achieved rapidly and with good chemoselectivity.

We reasoned that the sulfations could be achieved more rapidly and perhaps more chemoselectively by using a base that was stronger than Et_3N and so generate a higher concentration of the phenoxide anion. We wished to avoid the use of very strong bases, such as *t*-BuOK, NaH, NaHMDS, etc., and so focused on DBU. Using estrone (**6**, Table 1) as a model substrate we initially attempted the sulfation by adding 1 equiv of DBU to a solution of estrone in dry CH_2Cl_2 followed by the addition of 1.1 equiv **1** or $TFEOSO_2Cl$ (**7**). However, after several hours the reaction had not gone to completion. In contrast, when the reaction was performed using 1.1 equiv of imidazolium salts **4** and **5** compounds **8**[10] and **9**[14] were obtained in almost quantitative yields in just 5 min (Table 1, entries 1 and 2). Similar results were found with estrone derivatives **10** and **12**

Table 2
Polysulfation of phenols using reagents **4** and **5** and DBU

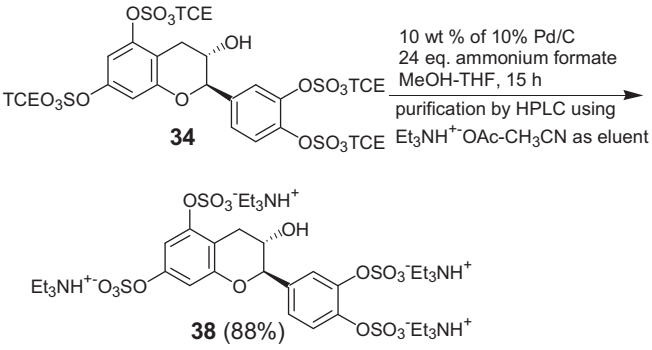
Entry	Substrate	Conditions	Product	% Yield
1 2	 **26**	2.2 equiv **4** or **5** 2.0 equiv DBU CH_2Cl_2, 13 min	 **27**, R = TCE **28**, R = TFE	93 (**27**) 91 (**28**)
3	 **29**	3.3 equiv **4** 3.0 equiv DBU CH_2Cl_2, 16 min	 **30**	90
4	 **31**	3.3 equiv **4** 3.0 equiv DBU CH_2Cl_2, 16 min	 **32**	96
5	 **33**	4.4 equiv **4** 4.0 equiv DBU CH_2Cl_2–DMF 19 min	 **34**	86
6 7	 **35**	5.5 equiv **4** or **5** 5.0 equiv DBU DMF 22 min	 **36**, R = TCE **37**, R = TFE	90 (**36**) 92 (**37**)

(entries 3 and 4). We also found that no drying of the CH_2Cl_2 was necessary in order to obtain equivalent yields in the same reaction times. Applying this methodology to estradiol resulted in almost exclusive sulfation of the phenolic OH in excellent yield (entry 5). Estriol (**14**) and the β-17-amino steroid **16** were also sulfated at the phenolic OH in excellent yields (entries 6 and 7). Due to the poor solubility of the DBU salt of estriol in CH_2Cl_2 this reaction had to be carried out in a DMF–CH_2Cl_2 mixture. Phenolic compounds **18** and **20** having a hydroxymethyl group at the meta and para positions were also sulfated chemoselectively at the phenolic OH in good yield (entries 8 and 9) as was hydroxyethyl derivative **24** (entry 11). However, when the phenolic hydroxyl and hydroxymethyl groups were ortho to one another a complex mixture was obtained (compound **22**, entry 10). All of the reactions in Table 1 were complete within 3–10 min. We found that there was no need for an aqueous workup for reactions carried out in CH_2Cl_2 as the products could be purified by applying the reaction mixture directly to a silica gel column and eluting with EtOAc–hexane mixtures. Reactions carried out in DMF–CH_2Cl_2 were subjected to an aq workup to remove the DMF before chromatography.[17]

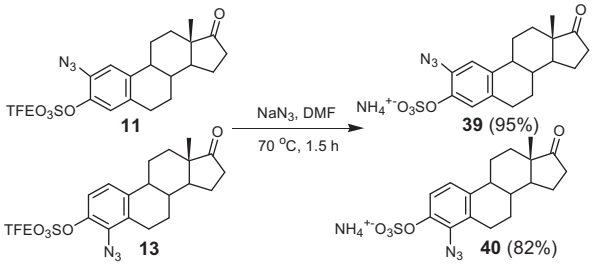
We next applied our methodology to the synthesis of multisulfated phenols and polyphenols. Several new approaches to such compounds have recently been reported. A high temperature (100 °C) microwave approach using SO_3–pyridine or amine complexes (NR_3 where R = Me or Et) has been developed.[18] This approach has been shown to work well in most cases though it requires 6–9 molar equiv of sulfating agent per phenolic group and is not amenable to scale-up. A low temperature (−20 to 20 °C), triflic acid-catalyzed (1.6–3.0 equiv/OH group) approach has been reported using SO_3–NEt_3 complex (5 molar equiv per OH group).[19] Desai and coworkers reported using reagent **1** for preparing multisulfated phenols and polyphenols.[11k] The reactions were conducted in anhydrous THF in the presence of Et_3N and DMAP for 16 h. In most cases, the desired compounds were obtained in excellent yield including a compound containing a crowded 1,2,3-trisulfated structure, which is almost impossible to isolate using traditional sulfation protocols and obtained in modest yield using the microwave approach.[18] Two- to four-fold molar excess of reagent **1** per OH group was required to fully sulfate pentahydroxy flavones possibly due to the presence of moisture tightly bound to the flavonoids substrates causing hydrolysis of **1**.

We have found that reagents **4** and **5** are very effective for the synthesis of multisulfated phenols and polyphenols (Table 2). These sulfations were achieved by adding 1.0 equiv of DBU to a solution of the substrate in CH_2Cl_2, DMF or CH_2Cl_2–DMF mixtures followed by the addition of 1.1 equiv **4** or **5** and stirred for about 3 min and then this process was repeated for each OH group. After the final addition the mixture was stirred for an additional 10 min. In most cases, the use of dry solvents was unnecessary and no aqueous workup was required for reactions carried out in the absence of DMF cosolvent. Compounds containing the three adjacent hydroxy groups were sulfated in excellent yield (entries 3 and 4). Compound **33** was chemoselectively sulfated at all four phenolic OH's leaving the secondary aliphatic OH untouched (entry 5). Sulfation of pentahydroxy flavone **35** was previously accomplished in 82% yield in 16 h using 4 equiv reagent **1** per OH group.[11k] We accomplished its synthesis in 90% yield in just 22 min using 1.1 equiv reagent **4** per OH group.[20]

It has been shown that trichloroethyl-protected multisulfated phenols such as **36** can be readily deprotected using Pd/C and excess ammonium formate.[11k] We also found this to be the case as demonstrated by the deprotection of **34** in excellent yield (Scheme 2). However, attempts to deprotect compounds containing multiple TFE-protected sulfates **28** and **37** using *t*-BuOK in refluxing *t*-BuOH or with NaN_3 in warm DMF was unsuccessful as these compounds decomposed upon heating. Compounds containing a single TFE-protected sulfate, such as compounds **11** and **13**, were deprotected in good yield using NaN_3 in warm DMF (Scheme 3).



Scheme 2. Deprotection of **35**.



Scheme 3. Deprotection of **11** and **13**.

In summary, we have shown that protected aryl sulfates can be prepared rapidly and in excellent yields using sulfuryl imidazolium salts **4** and **5** and DBU. The sulfate groups could be introduced into phenolic hydroxyl groups in the presence of aliphatic hydroxyls with high chemoselectivity. Multiple sulfations were also readily achieved using just a slight excess of sulfating agent per hydroxyl group.

Acknowledgment

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Supplementary data

Additional experimental details and characterization data and ^1H and ^{13}C NMR spectra for all novel compounds. Experimental details for the synthesis of **38**–**40**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.080.

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17. *Representative procedure for monosulfations: Synthesis of compound* **3**. To a suspension of estradiol (**2**) (0.136 g, 0.5 mmol) in CH_2Cl_2 (3 mL) was added 1 equiv DBU. The mixture was stirred until it became homogeneous (approximately 10 min). Reagent **4** (0.254 g, 0.55 mmol) was added in three portions over 1 min and the mixture stirred for an additional 4 min. The mixture was applied directly to a silica column prepared using 30% EtOAc:70% hexane. Elution with the same solvent system (R_f = 0.3) gave pure **3** as a white solid (0.211 g, 90% yield). Mp = 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.10–1.60 (m, 7H), 1.11–1.58 (m, 7H), 1.68 (dd, *J* = 8.8, 13.1 Hz, 1H), 1.77–2.35 (m, 6H), 2.84 (br s, 2H), 3.70 (t, *J* = 7.8 Hz, 1H), 4.80 (s, 2H), 7.02 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 23.1, 26.1, 26.8, 29.5, 30.5, 36.6, 38.3, 43.2, 44.1, 50.0, 80.3, 817, 92.5, 117.9, 121.0, 127.0, 139.3, 140.3, 147.9; HRMS (EI$^+$): calcd for $C_{20}H_{25}Cl_3O_5S$ (M^+): 482.0488, found 482.0491.
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20. *Representative procedure for multisulfations: Synthesis of compound* **36**. To a solution **35** (0.05 g, 0.17 mmol) in dry DMF (3 mL) was added 1 equiv DBU. Reagent **4** (0.076 g, 0.182 mmol) was added and the mixture was stirred for approximately 3 min. This process was repeated four more times. After the final addition the mixture was stirred for 10 min then diluted with Et_2O (30 mL) and washed with 0.1 N HCl, water and satd brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (30% EtOAc:70% hexane, R_f = 0.5) to give pure **36** as a white foam (0.203 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 2H), 4.96 (s, 2H), 4.97 (2, 2H), 5.14 (s, 2H), 5.17 (s, 2H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.05 (dd, *J* = 1.7, 8.8 Hz, 1H), 8.17 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.1, 81.2, 81.4, 91.7, 92.0, 92.2, 110.7, 114.0, 116.4, 123.7, 123.9, 128.5, 129.6, 134.2, 141., 143.8, 148.4, 153.0, 156.1, 156.5, 168.7; HRMS (ESI$^+$): calcd for $C_{25}H_{16}Cl_{15}O_{22}S_5$ (M+H): 1352.406, found 1352.387.