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Efficient general method for sulfamoylation of a hydroxyl group

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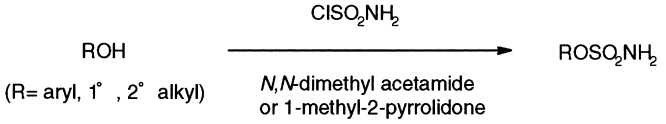
Abstract

The application of *N*,*N*-dimethylacetamide or 1-methyl-2-pyrrolidone as solvent clearly accelerated the sulfamoylation reaction of a hydroxyl group compared with the solvents used so far. The target sulfamates were obtained in the highest yield without a base. It became clear that 2 equiv. of sulfamoyl chloride to the starting material was sufficient to complete the reaction. It was confirmed that this condition could be applied to extensive hydroxyl groups.

Keywords: solvents and solvent effects; phenols; alcohols; sulfamoylation; sulfamic acid and derivatives.

Some important biological activities have been reported for the sulfamoyloxy group, for example, potential antitumor in the steroid,[1] antibiotic in the nucleoside[2] and antiepilepsy in the sugar.[3] However, in the sulfamoylation so far, excessive base and sulfamoyl chloride[4] were used and the yields were often inadequate.[1d,2a,d,3a,b] Moreover, when *N*,*N*-dimethylformamide (DMF) was used as a solvent, the undesired DMF adduct was obtained.[1c] This time we solved these problems by using readily available and highly solubilizing *N*,*N*-dimethylacetamide (DMA) or 1-methyl-2-pyrrolidone (NMP) as a solvent (Eq. (1)). We optimized the reaction conditions and found that the amounts of a base and sulfamoyl chloride were important to attain a high yield. We confirmed that this method could be applied to extensive alcohols and phenols.



(1)

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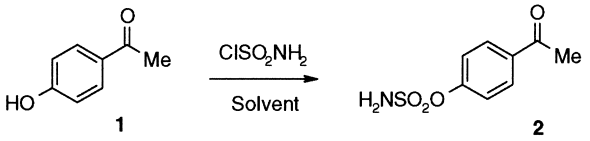
First, we examined the reaction of 4-hydroxyacetophenone (**1**) and sulfamoyl chloride in various solvents (Eq. (2) and Table 1). We found that the solvent had great influence on the rate of reaction. The rate was slow in a previously reported solvent, 1,2-dimethoxyethane (DME),[2a,d] dichloromethane[1c] or DMF[1b,c,d,3b] (runs 1–3). To the contrary, the rate in NMP or DMA was faster with minimal by-product formation (runs 4 and 5). Considerable reaction progress in NMP or DMA as well as in DMF probably reveals that these solvents work as moderate bases. The diminished rate for DMF, compared with NMP or DMA, possibly attributes to a competing reaction between DMF and sulfamoyl chloride. Formyl proton in DMF was changed to carbon in DMA or NMP (Fig. 1), so DMA or NMP might have an inadequate reactivity for the competing reaction.



(2)

Table 1
Conversion of **1** into **2** in various solvents[a]

Run	Solvent	Recovery of **1**, (%)[b]	Yield of **2**, (%)[b]
1	DME[c]	91	0.0
2	CH_2Cl_2	81	4.9
3	DMF[d]	34	60
4	NMP[e]	0.9	94
5	DMA[f]	0.2	98

[a] Sulfamoyl chloride (4.0 mmol) was added to a stirred mixture of 4-hydroxyacetophenone (1.0 mmol) and solvent (1.5 mL) on ice-cooling. The mixture was then stirred at room temperature for 3 h.
[b] Calculated based on HPLC analysis
[c] DME: 1,2-dimethoxyethane; [d] DMF: *N,N*-dimethylformamide;
[e] NMP: 1-methyl-2-pyrrolidone; [f] DMA: *N,N*-dimethylacetamide

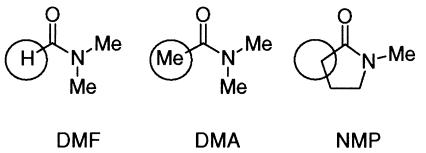


Figure 1.

Next, we examined the amounts of the bases used (Table 2). Interestingly, elimination of a base led to the highest yield (run 1). Probably DMA worked as a moderate base. When the base was excessively used, the yield was diminished (runs 2–4). This was because further sulfamoylation of the sulfamoyl group[1c,5] and decomposition of sulfamoyl chloride[6] might have occurred in the presence of base. It has already been reported that sulfamoylation of estrone proceeded in DMF

Table 2
Conversion of **1** into **2** with various amounts of triethylamine[a]

Run	Triethylamine (equiv.)	Recovery of **1**, (%)[b]	Yield of **2**, (%)[b]
1	0.0	0.2	98
2	1.3	0.1	96
3	4.0	2	73
4	6.0	18	55

[a] Triethylamine was added to a stirred mixture of 4-hydroxyacetophenone (1.0 mmol) and DMA (1.5 mL) on ice-cooling. The mixture was stirred for 30 min and sulfamoyl chloride (4.0 mmol) was added. The mixture was then stirred at room temperature for 3 h.
[b] Calculated based on HPLC analysis

without any additional base.[1c] However, 5 equiv. of sulfamoyl chloride and 12 hours of reaction time were needed for completion of the reaction. Our method needed only 2 equiv. of sulfamoyl chloride and 3 hours of reaction time (Table 4, runs 3 and 4).

As for the amounts of sulfamoyl chloride, we found that the more sulfamoyl chloride was used, the faster the rate was (Table 3, runs 1–3). Conventionally, 5–6 equiv. of sulfamoyl chloride have been used.[1c,d] But our method needs only 2 equiv. of sulfamoyl chloride to the starting material to complete the reaction, because our condition does not include any base and DMF, which waste sulfamoyl chloride as we have mentioned above.

Table 3
Conversion of **1** into **2** with various amounts of sulfamoyl chloride[a]

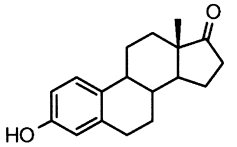
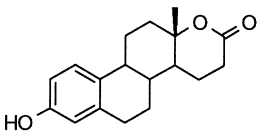
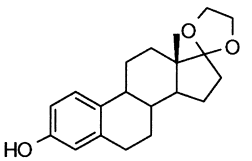
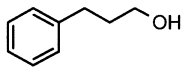
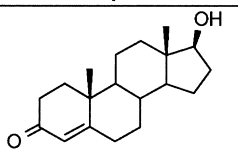
Run	Sulfamoyl Chloride, (equiv.)	Recovery of **1**, (%)[b]	Yield of **2**, (%)[b]
1	1.0	14	86
2	2.0	0.7	97
3	4.0	0.2	98

[a] Sulfamoyl chloride was added to a stirred mixture of 4-hydroxyacetophenone (1.0 mmol) and DMA (1.5 mL) on ice-cooling. The mixture was then stirred at room temperature for 3 h.
[b] Calculated based on HPLC analysis

An application of this reaction condition is summarized in Table 4.[7] It was confirmed that phenols with an electron-withdrawing or donating group, ketone, lactone or ketal smoothly reacted to give good yield (runs 1–6). Even fatty alcohols (primary, secondary) went well (runs 7–9). But a tertiary alcohol did not afford the corresponding sulfamate,[8] probably because of occurrence of β-elimination. A reaction using NMP as a solvent gave a similar result to DMA (runs 4 and 8).

In conclusion, we have developed a general method to effectively convert a hydroxyl group to a sulfamoyloxy group using a minimum amount of the reagent. This method has the advantage of being applicable to extensive alcohols and phenols at low cost and with a convenient operation as compared with the former method. It was also successful in the scale-up to 21 g (75 mmol) of **5** (Table 4, run 5).[9] This method will be useful not only in the laboratory but also for industrial manufacture.

Table 4
Application of this method to various substrates[a]

Run	Starting Material	Reaction Time, (h)	Solvent	Isolated Yield of Sulfamate, (%)
1	4-(HO)C_6H_4COMe (**1**)	3	DMA	91
2	4-(HO)C_6H_4OMe (**3**)	3	DMA	92
3	 **4**	3	DMA	94
4			NMP	96
5	 **5**	6	DMA	89
6	 **6**	3	DMA	86
7	 **7**	3	DMA	85
8			NMP	93
9	 **8**	3	DMA	91

[a] Sulfamoyl chloride (2.0 mmol) was added to a stirred mixture of a hydroxyl compound (1.0 mmol) and solvent (1.5 mL) on ice-cooling. The mixture was then stirred at room temperature.

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5. In the presence of base, sulfamoyl sulfamate (**9**) might have to be generated as a by-product:[1c] 4-($H_2NSO_2NHSO_2O$)C_6H_4COMe (**9**).
6. Sulfamoyl chloride decomposed gradually in the presence of base in NMP. To the contrary, sulfamoyl chloride hardly decomposed in only NMP.
7. General procedure: Sulfamoyl chloride (2.0 mmol) was added to a stirred mixture of a hydroxyl compound (1.0 mmol) and DMA (1.5 mL) on ice-cooling. The mixture was then stirred at room temperature for 3 hours. The mixture was poured into cold brine, and the resulting solution was extracted with ethyl acetate (2×20 mL). The organic layer was separated, washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified by TLC. **4-Acetylphenyl sulfamate**: MS *m*/*e*: 215 (M^+), 136, 121; ^{1}H NMR (DMSO-d_6, δ): 2.58 (3H, s), 7.3–7.5 (2H, m), 8.0–8.1 (2H, m), 8.15 (2H, s). **4-Methoxyphenyl sulfamate**: MS *m*/*e*: 203 (M^+), 123; ^{1}H NMR (DMSO-d_6, δ): 3.76 (3H, s), 6.9–7.0 (2H, m), 7.1–7.3 (2H, m), 7.83 (2H, s). **17-Oxoestra-1,3,5(10)-trien-3-yl sulfamate**: MS *m*/*e*: 349 (M^+), 270; ^{1}H NMR (DMSO-d_6, δ): 0.84 (3H, s), 2.87 (2H, dd, J = 3.8, 8.6 Hz), 6.98 (1H, d, J = 2.4 Hz), 7.02 (1H, dd, J = 2.4, 8.5 Hz), 7.35 (1H, d, J = 8.5 Hz), 7.86 (2H, s). **17-Oxo-17a-homo-17a-oxaestra-1,3,5(10)-trien-3-yl sulfamate**: MS *m*/*e*: 365 (M^+), 286; ^{1}H NMR (DMSO-d_6, δ): 1.28 (3H, s), 1.4–1.7 (2H, m), 1.78 (1H, dt, J = 3.5, 13.0 Hz), 1.9–2.1 (3H, m), 2.6–2.8 (1H, m), 2.7–3.0 (2H, m), 6.98 (1H, d, J = 2.6 Hz), 7.03 (1H, dd, J = 2.6, 8.5 Hz), 7.36 (1H, d, J = 8.6 Hz), 7.88 (2H, s). **17,17-(Ethylenedioxy)estra-1,3,5(10)-trien-3-yl sulfamate**: MS *m*/*e*: 393 (M^+), 348, 314, 269; ^{1}H NMR (DMSO-d_6, δ): 0.81 (3H, s), 2.1-2.3 (1H, m), 2.3-2.4 (1H, m), 2.7-2.9 (2H, m), 3.7-3.9 (4H, m), 6.96 (1H, d, J = 2.5 Hz), 7.01 (1H, dd, J = 2.5, 8.5 Hz), 7.33 (1H, d, J = 8.5 Hz), 7.85 (2H, s). **3-Phenylpropyl sulfamate**: MS *m*/*e*: 215 (M^+), 117; ^{1}H NMR (DMSO-d_6, δ): 1.8–2.0 (2H, m), 2.66 (2H, t, J = 7.7 Hz), 4.02 (2H, t, J = 6.4 Hz), 7.1–7.4 (5H, m), 7.41 (2H, s). **3-Oxoandrost-4-en-17β-yl sulfamate**: MS *m*/*e*: 367 (M^+), 270; ^{1}H NMR (DMSO-d_6, δ): 0.78 (3H, s), 1.16 (3H, s), 4.25 (1H, t, J = 8.4 Hz), 5.62 (1H, s), 7.32 (2H, s).
8. The reaction of 2-phenyl-2-propanol showed conversion to a less-polar product (on TLC), but we could not isolate any non-volatile materials.
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