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Mild and Safer Preparative Method for Nonsymmetrical Sulfamides via *N*-Sulfamoyloxazolidinone Derivatives: Electronic Effects Affect the Transsulfamoylation Reactivity

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Abstract:

Sulfamides ($R_1R_2N-SO_2-NR_3R_4$) are traditionally prepared by using strong electrophilic and hazardous reagents such as *N*-sulfamoyl chloride, sulfonyl chloride, phosphorus oxychloride, or phosphorus pentachloride. We report here a safer and more convenient synthetic methodology for large-scale preparation of sulfamides using the N-substituted oxazolidin-2-one derivatives 5 as synthetic equivalent of the corrosive and hazardous *N*-sulfamoyl chloride. The scope of the use of *N*-sulfamoyloxazolidinones to prepare nonsymmetrical sulfamides is explored.

Introduction

Sulfamides represent an important class of pharmaceutically active molecules in many therapeutic areas such as HIV protease inhibitors, nonhydrolyzable components in peptidomimetics as well as interesting intermediates in the agrochemical industries.

Symmetrically substituted sulfamides ($RR'NSO_2NRR'$) are typically prepared by reacting strong electrophilic reagents such as SO_2Cl_2 and the corresponding amine.

The most commonly used preparative methods for unsymmetrically substituted sulfamides rely in general on a synthetic route involving the reaction between the *N*-sulfamoyl chloride[1] derivatives and the appropriate amine.[2] Typical preparation of sulfamoyl chlorides uses strongly hazardous and corrosive materials such as fuming sulfuric acid, isocyanate derivatives, phosphorus pentachloride, or sulfuryl chloride, as exemplified by the preparation of *i*-$PrNHSO_2Cl$ (**1**, Scheme 1).[3]

During the development of a process for the preparation of sulfamide **3** (Scheme 2) via the reaction of the aromatic amine **2** with the *i*-$PrNHSO_2Cl$, **1**, we discovered a severe thermal hazard during the purification by distillation of **1**. Indeed, the thermal analysis of the distillation residue shows a runaway for which the onset was 10 °C higher than the reaction mixture distillation temperature (Figure 1).

This event triggered the development of a safer preparative method of the nonsymmetrical sulfamide **3**.

Several other synthetic methodologies are reported such as transamidation of monosubstituted sulfamides,[5] the stepwise addition of *tert*-butyl alcohol and a primary amine to chlorosulfonylisocyanate (CSI),[6] followed by Mitsonobu reaction and removal of the BOC group[7] and the amination of aryl-substituted sulfamate esters.[8] More recently, Winum et al. described the preparation of a new sulfamoylating reagent (*N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide **4** (Scheme 3).[9]

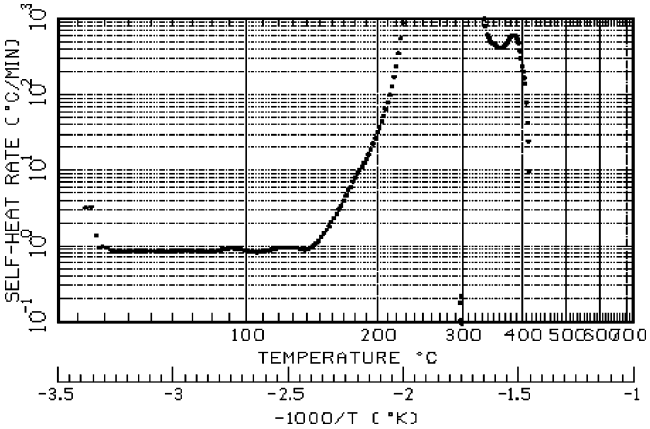

Figure 1. **Thermal analysis of distillate residue (RSST[4]).**

However, we found that an alternative methodology previously described by Montero et al.[10] using nonhazardous *N*-sulfamoyloxazolidinones **5** as transsulfamoylating agents (Scheme 4) provided a safe alternative to the use of sulfamoyl chloride derivatives. These oxazolidinones derivatives, **5**, are crystalline and thermally stable compounds.

To our knowledge, this methodology has not been extensively used for the preparation of nonsymmetrical sulfamides[11] and is limited to the preparation of various 2-chloroethylsulfamides.[12]

In this paper, we explore the scope of this synthetic method and apply it to the preparation of nonsymmetrical sulfamides of various substitution patterns (aromatic–aromatic, aliphatic–aliphatic, and aromatic–aliphatic). In

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(1) Kloek, J. A.; Leschinsky, K. L. *J. Org. Chem*. **1976**, *41*, 4028–4029.
(2) Timberlake, K. W.; Warren, J. R., Jr.; Stevens, E. S.; Klein, C. L. *J. Org. Chem*. **1989**, *54*, 5824–5826.
(3) BASF Belgian Patent No. 667,311, July 25, 1966.
(4) RSST = Reactive Systems Screening Tool (Fauske & Associates, LLC).
(5) McDermott, S. D.; Spillane, W. J. *Synthesis* **1983**, 192–195.
(6) Masui, T.; Kabaki, M.; Watanabe, H.; Kobayashi, T.; Masui, Y. *Org. Process Res. Dev*. **2004**, *8*, 408–410
(7) (a) Abdaoui, M.; Dewynter, G.; Aouf, N.; Favres, G.; Morère, A.; Montero, J. L. *Biorg. Med. Chem*. **1996**, *4*, 1227–1235. (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev*. **2004**, *104*, 2239–2258.
(8) DuBois, G. E. *J. Org. Chem*. **1980**, *45*, 5373–5375.
(9) Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241–2243.
(10) Montero, J. L.; Dewynter, G.; Agoh, B.; Delaunay, B.; Imbach, J. L. *Tetrahedron Lett*. **1983**, *24*, 3091–3094.
(11) Antoine, L.; Borghese, A.; Van Hoeck, J. P. PCT WO 01/36383 A1, 2001.
(12) Dewynter, G.; Abdaoui, M.; Regaina, Z. *Tetrahedron* **1996**, *52*, 14217–14224.

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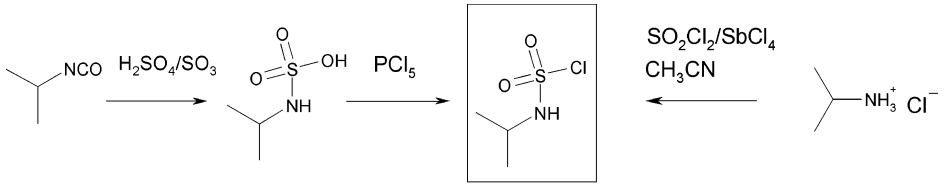
Scheme 1. **Preparation of *i*-PrNHSO$_2$Cl (1)**



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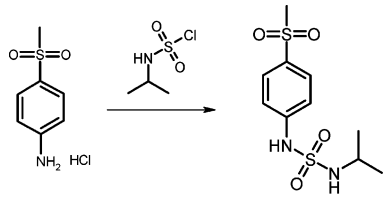
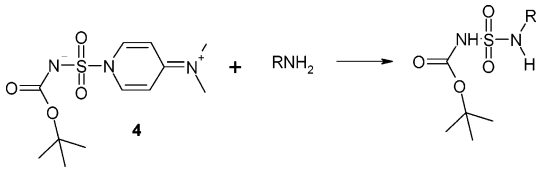
Scheme 2. **Preparation of sulfamide 3**



2 **3**

Scheme 3. **Use of 4 as sulfamoylating reagent**



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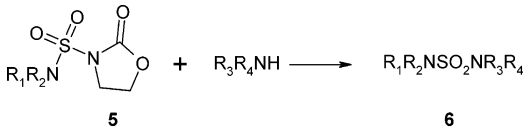
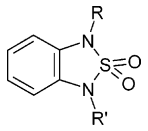
Scheme 4. **Use of oxazolidinones 5 as sulfamoylating agents**



5 **6**

R_1, R_2, R_3, R_4 = alkyl, aryl, H

addition this methodology has been extended to include the preparation of cyclic sulfamides, e.g., **7**, for which classical synthetic methodologies (reaction of sulfonyl urea (H_2NSO_2-NH_2) or SO_2Cl_2 with vicinal diamines[13,14]) failed to give the desired cyclosulfamides.



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Results and Discussion

The N-substituted oxazolidinones **5a**−**5h** (Table 1) were prepared in good yields according to the reported method (Scheme 5),[15] and reacted with various alkyl and aromatic amines to afford the corresponding nonsymmetrical sulfamides.

Chlorosulfonylisocyanate (CSI) was reacted with 2-halogenoethanol **8** followed by reaction of the in situ generated halogenosulfonyloxazolidinone **9** with the appropriate primary amine, in the presence of Et_3N to yield **5**.

All of the oxazolidinone derivatives **5** reported in Table 1 are crystalline and thermally stable compounds. These oxazolidinones derivatives **5** have been reacted (Scheme 4) with various primary amines in acetonitrile, in the presence of Et_3N to give good yields of the mixed aliphatic and aromatic sulfamides **6** listed in Table 2.

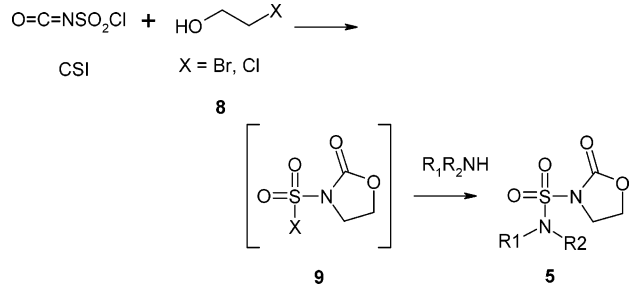
Due to the unreactivity of the oxazolidinone **5b** (entry 2, Table 1), the sulfamides **6b** and **6f** (entries 2 and 6, Table 2) have been prepared by reacting respectively the oxazolidinones **5h** and **5a** (entries 8 and 1, Table 1) with *i*-PrNH$_2$ and *p*-MeSO$_2$PhNH$_2$. The remaining sulfamides of Table 2 (**6a**, **6c**, **6d**, **6e**, and **6g**) have been obtained by reacting **5h** (entry 8, Table 1) with the appropriate amines.

Table 1. **Prepared oxazolidinone derivatives 5**

entry	oxazolidinones **5**	R_1	R_2	yield (%)[a]
1	**5a**	*p*-MePh	H	61
2	**5b**	*p*-MeSO$_2$Ph	H	89
3	**5c**	*p*-NO$_2$Ph	H	69
4	**5d**	*p*-ClPh	H	46
5	**5e**	Ph	H	96
6	**5f**	Me	H	39
7	**5g**	Et	Et	65
8	**5h**	*i*-Pr	H	71

[a] Yields are not optimized

Scheme 5. **Preparation of oxazolidinone derivatives 5**



8 **9** **5**

Table 2. **Mixed aliphatic and aromatic sulfamides 6 ($R_1R_2NHSO_2NR_3R_4$)**

entry	sulfamides **6**	R_1	R_2	R_3	R_4	yield (%)
1	**6a**	p-MePh	H	*i*-Pr	H	74
2	**6b**	p-MeSO$_2$Ph	H	*i*-Pr	H	85
3	**6c**	*p*-MeSPhe	H	*i*-Pr	H	62
4	**6d**	p-ClPh	H	*i*-Pr	H	84
5	**6e**	Ph	H	*i*-Pr	H	87
6	**6f**	p-MeSO$_2$Ph	H	p-MePh	H	68
7	**6g**	*i*-Pr	H	*t*-amyl	H	73

(13) Lawson, A.; Tinkler, R. B. *Chem. Rev.* **1970**, *70*, 593−618.
(14) Rosenberg, S. H.; Dellaria, J. F.; Kempf, D. J.; Hutchins, C. W.; Woods, K. W.; Maki, R. G.; de Lara, E.; Spina, K. P.; Stein, H. S.; Cohen, J.; Baker, W. R.; Plattner, J. J.; Kleinert, H. D.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 1582−1590.
(15) Abdaoui, M.; Dewynter, G.; Montero, J. L. *Tetrahedron. Lett.* **1996**, *37*, 5695−5698.

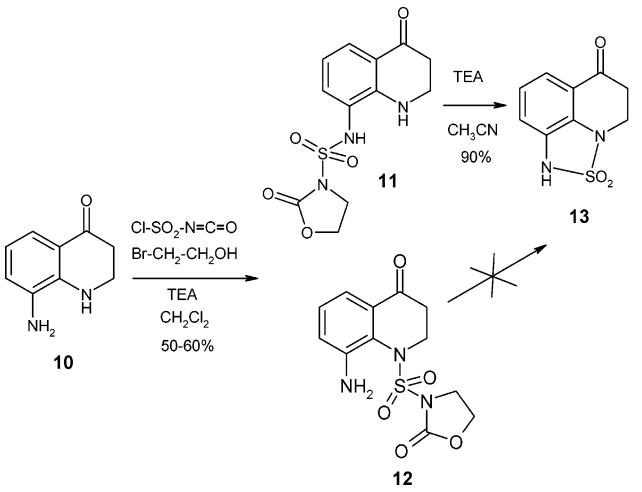


Figure 2. **Example of synthesis of cyclic sulfamide 13.**

Similarly, **5c** failed to react with primary amines to yield the corresponding sulfamides.

Attempts to use **5g** (entry 7, Table 1) to prepare sulfamide types $R_1R_2NSO_2NHR_3$ (R1, R2, R3 ≠ H) failed to give the desired product.

An example of this synthetic methodology applied to the preparation of the cyclic sulfamide **13** is shown in Figure 2.

A 75:25 mixture of isomers **11**:**12** have been obtained. Ring closure of **11** performed in CH_3CN in the presence of Et_3N gives **13** with 90% yield.

The other oxazolidinone isomer **12**, resulting from the reaction of intermediate **9** with the secondary amine of **10**, failed to cyclize to give **13**, displaying the same unreactivity as that shown by **5g** (Table 1, entry 7). In contrast, the reaction of the *vic*-diamine **10** failed to react with the $H_2NSO_2NH_2$ to give the cyclic sulfamide **13**.

During this work, we found some limitations to the application of this methodology when strong electron-withdrawing (EW)-substituted aromatic oxazolidinones **5** (Table 1, entries 2 and 3, R = *p*-$MeSO_2Ph$, *p*-NO_2Ph) are used. In this case, the transsulfamoylating reactivity was lost, thus preventing their use for the preparation of symmetrical or unsymmetrical EW-substituted aromatic sulfamides.[16] As a consequence, the preparation of unsymmetrical mono-EW-substituted aromatic sulfamides requires reacting the oxazolidinone derivative **5** prepared from the amine moiety R_3NH_2, which does not bear the EW substituent. This methodology is therefore not suited for preparing bis-EW-substituted sulfamides.

We tentatively rationalize the observed EW-substituent effect via a preliminary mechanistic insight of the transsulfamoylation reaction.

(16) With an EW-substituted aromatic oxazolidinone, ring opening of the oxazolidinone moiety occurred by reaction with the secondary amine to yield the carbamate derivative **14**.

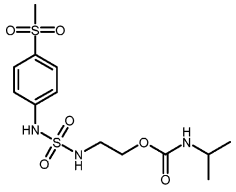


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Table 3. **First-order rate constant at various 5h concentrations**

$10^4[\mathbf{5h}]_0$ (mol dm^{-3})	k^I (min^{-1})
3.22	2.6610^{-3}
4.83	$2.60\ 10^{-3}$
6.44	$2.85\ 10^{-3}$
12.90	$2.60\ 10^{-3}$

Mechanism of the Transsulfamoylation Reaction. An elimination mechanism (E1cB) of reaction proceeding via the very electrophilic *N*-sulfonylamine RN═SO_2 species was established when sulfamoyl chlorides ($RNHSO_2Cl$) were used to prepare sulfamides.[17] Analogously, the same mechanism of reaction was demonstrated for the aminolysis and hydrolysis of sulphate ester derivatives[18] and was also hypothesized by Dewynter[12] when using oxazolidinone derivatives to prepare the desired sulfamide. Deprotonation of **5** under basic conditions (Et_3N) generates presumably the transient very electrophilic *N*-sulfonylamine RN═SO_2 species[19] which further reacts with the amine to afford the sulfamide **6**. The unreactivity of the di-N-substituted oxazolidinones **5g** (Table 1) and **12** (Figure 2) as sulfamoylating agent provides a first evidence supporting a mechanism triggered by first deprotonation of **5**.

Kinetic Analysis. ^{1}H NMR and HPLC kinetic runs were carried out by reacting **5h** with aniline and the substituted anilines in acetonitrile in the presence of Et_3N as catalyst at 70 °C.

The following preliminary kinetic results support the hypothesis that the formation of sulfamides is first preceded by the formation of an intermediate in the rate-determining step, followed by a fast reaction of the intermediate with the selected amine to yield the sulfamide. The kinetics are first order in **5h** since identical rates (determined from first-order plots) were obtained for various **5h** concentrations (Table 3).

The kinetics of transsulfamoylation is also affected by the Et_3N concentration (Figure 3). However, no formal order was established for Et_3N.

We found that the kinetics of formation of sulfamide **6e** was insensitive to the aniline concentration (Figure 4). Likewise, the kinetics of formation of the corresponding sulfamides from **5h** is independent of the type of aniline (Figure 5, Table 4: identical first-order rates were obtained for H-, *p*-Cl- and *p*-Me-, *p*-NO_2-, and *p*-$MeSO_2$-substituted anilines). Departure from a first-order behavior together with a rate decrease is observed over time for EW-substituted aniline (*p*-$MeSO_2$ and *p*-NO_2). This is due to the acid−base consumption of the catalyst (Et_3N) by the formed acidic sulfamides.[20] In this case the initial first-order rates were

(17) Spillane, W. J.; McHugh, F. A.; Burke, P. O. *J. Chem. Soc., Perkin Trans. 2* **1998**, *1*, 13−18

(18) Spillane, W. J.; Hogan, G.; McGrath, P. *J. Phys. Org. Chem.* **1995**, *8*, 610−616.

(19) (a) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1967**, *89*, 2502; Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744; Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 6135. (b) Burgess, E. M.; Williams, W. M. *J. Am. Chem. Soc.* **1972**, *94*, 4386. (c) Kloek, J. A.; Leschinsky, K. L. *J. Org. Chem.* **1976**, *44*, 4028.

(20) A pK_a of 11 has been determined for sulfamide **3b** in acetonitrile.

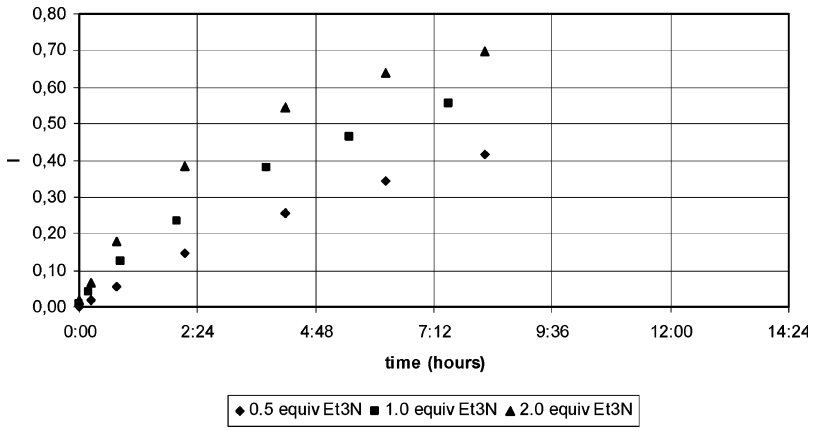


Figure 3. **Effect of Et_3N concentration on the kinetic of formation of 6e. I = integrated ^1H NMR signal of aromatic protons of 6e at 7.19 ppm (d, 2H).**

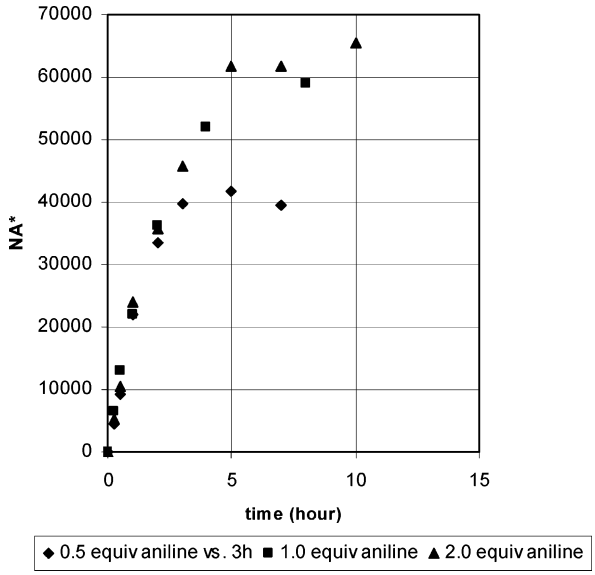


Figure 4. **Effect of aniline concentration on the kinetic of formation of 6e. *NA = HPLC absolute area of 6e normalized by sample weight.**

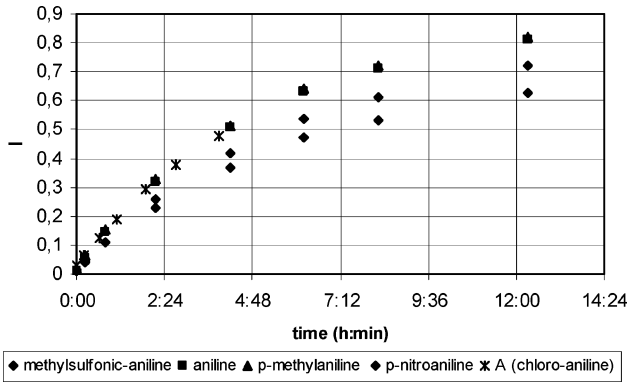


Figure 5. **Effect of substituted anilines on the kinetic of formation of the corresponding sulfamide from 5h. *I = integrated ^1H NMR signal of the aromatic protons of formed sulfamides in acetonitrile.**

Table 4. **First-order rate constants (effect of substituted anilines) of formation of the corresponding sulfamides from 5h**

aniline	$10^3 \times k^I$ (min^{-1})	$10^3 \times k^I_0$ (min^{-1})
p-$MeSO_2$	–	2.6
p-NO_2	–	2.6
p-Cl	2.8	
H	2.6	
p-Me	2.6	

measured (Table 4). Addition of an initial amount (20%) of **6b** decreases the initial rates of formation (from $k_0^I = 2.6 \times 10^{-3}$ min^{-1} to 1.2×10^{-3} min^{-1}) of sulfamide **6b**, thus confirming the hypothesis.

Although not formally proven, the intermediate postulated during the transsulfamoylation reaction is likely the *N*-sulfonylamine species **d** (Scheme 6) as postulated by several authors for similar transsulfamoylation reactions. Formation of that intermediate is preceded by the deprotonation of the *N*-sulfamoyloxazolidinone **5** to give species **a (**Scheme 6**)**. Anion **a** is stabilized through either mesomeric forms **c** or **b**, depending on the EW force of both functional groups attached on the nitrogen atom. We can reasonably postulate that only form **b** will lead to the formation of the *N*-sulfonylamine intermediate. Given that mechanism of reaction and hypothesis, we can therefore tentatively rationalize the loss of transsulfamoylation reactivity of EW-substituted aromatic oxazolidinone by assessing which mesomeric forms **b** or **c** (Scheme 6) will be the more likely.

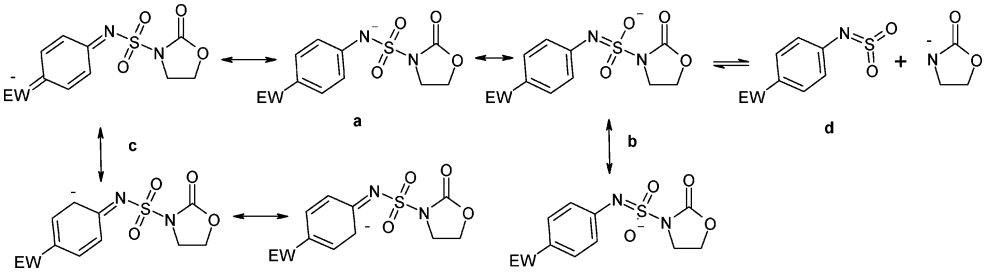
A way to roughly assess which mesomeric form will predominate between **c** and **b** is provided by the Hammet substituent constants.[21] The *p*-$MeSO_2$ ($\sigma_p = +0.72$) and the NO_2 ($\sigma_p = +0.78$) substituents, being more electron withdrawing than the SO_2-oxazolidinone moiety (assessed by analogy with the $SO_2N(Me)_2$, $\sigma_p = +0.65$), will stabilize **a** by delocalization of the nitrogen negative charge into the aromatic system, stabilizing form **c**, and thus hampering the transulfamoylation reaction.

This reasoning is further supported by the fact that the less EW (Cl, $\sigma_p = +0.23$) *p*-Cl-phenyl-substituted oxazolidinone reacts with the *i*-$PrNH_2$ to give the unsymmetrical sulfamide (Table 2, entry 4). In this case, form **b** would be the more likely mesomeric form.

Bis-EW-substituted aromatic sulfamides are better prepared by reacting the appropriate phenyl-substituted sulfa-

(21) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

Scheme 6. **Mesomeric forms involved in the formation of d**



moyl chloride (X-PhNHSO$_2$Cl) with the required substituted aniline, due to the highest EW property ($\sigma_p = +1.11$) of the SO_2Cl functional group, which therefore favors the formation of the *N*-sulfonylamine species and thus its subsequent reaction with the amines.

Conclusions

The use of the *N*-sulfamoyloxazolidinone derivatives was proven to be versatile for the preparation of symmetrical and unsymmetrical aliphatic and aromatic sulfamides. It provides a safer alternative to the use of sulfamoyl chloride for the construction of the nonsymmetrical sulfamide moieties on large scale.

However, a limitation was found when bis-EW sulfamide has to be prepared by this synthetic methodology. In this case, use of other synthetic methodologies referenced in the Introduction will be more suited to avoid the safety issue associated with the large-scale preparation of *N*-sulfamoyl chloride derivatives.

Experimental Section

General. Starting materials were obtained from commercial suppliers and were used without further purification. Kinetics of transsulfamoylation were performed at 70 °C in CH_3CN and followed by ^{1}H NMR at 250 MHz and by HPLC. Before use, aniline was purified by distillation over NaOH under reduced pressure. The substituted anilines were used without further purification. **5h** was purified by crystallization and used as the transsulfamoylating agent for the kinetic study. Chemical shifts are expressed in δ values with respect to TMS.

Typical Operating Procedure for Synthesis of the Oxazolidinone 5h. To a 250-L glass-lined reactor initially charged with dichloromethane (42 L) was added chlorosulfonyl isocyanate (4.5 kg, 31.8 mol) at room temperature and under a nitrogen atmosphere. The reaction mixture was cooled to about 1 °C, and a solution of 2-bromoethanol (4.00 kg, 32 mol, 1 equiv) in dichloromethane (14 L) was slowly added over 50 min to keep the reaction temperature between 0 and 10 °C. Stirring of the reaction mixture was continued at the same temperature for a minimum of 30 min. Progress of the reaction was monitored by ^{1}H NMR. A mixture of isopropylamine (2.1 kg, 35.5 mol, 1.1 equiv) and triethylamine (7.1 kg, 70.16 mol) in dichloromethane (28 L) was then added at such an addition rate that the reaction temperature was maintained between 0 and 10 °C. The solution was heated to room temperature. Aqueous hydrochloric acid (0.2 N, 28.5 kg) was then added, and the pH of the reaction mixture was adjusted to about 2 by addition of concentrated hydrochloric acid (450 mL in two portions). The reaction mixture was decanted and the separated organic layer washed with aqueous hydrochloric acid (28.1 kg, 0.05 N). Then the decanted and separated organic layer was washed with water (28 kg). To the decanted and separated organic layer, was then added water (28 kg), and the reactor was placed under vacuum to distill the maximum of dichloromethane while controlling the temperature below 25 °C (84.4 kg of distillate). The resulting suspension was stirred for a minimum of 2 h at room temperature, filtered, rinsed twice with water (2 × 7 L), and dried under vacuum at about 50 °C during 16 h to afford the 2-oxo-oxazolidine-3-sulfonic acid isopropyl-amide **5h** (4.38 kg, 21.0 mol, 66.2%). Mp 107−108 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, J = 6.6 Hz, 6H), 3.65 (m, J = 6.6 Hz, 1H), 4.08 (dd, J = 6.6, 8.5, 2H), 4.44 (dd, J = 7.6, 9.4 Hz, 2H), 5.22 (br d, J = 5.7 Hz, 1H). Anal. Calcd for $C_6H_{12}N_2O_4S$: C, 34.61; H, 5.81; N, 13.45; S, 15.40. Found: C, 34.82; H, 5.46; N, 13.23; S, 15.66.

5a: ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.26 (s, 3H), 3.85 (dd, J = 6.6, 8.5 Hz, 2H), 4.28 (dd, J = 7.5, 9.4 Hz, 2H), 7.09 (dm, J = 8.5 Hz, 2H), 7.12−7.19 (dm, J = 8.2 Hz, 2H), 10.83 (s, 1H). Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.867; H, 4.719; N, 10.931; S, 12.511. Found: C, 46.86; H, 4.66; N, 10.90; S, 12.49.

5b: ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.18 (s, 3H), 4.07 (dd, J = 6.0, 8.2 Hz, 2H), 4.38 (dd, J = 7.2, 8.5 Hz, 2H), 7.38 (dm, J = 8.8 Hz, 2H), 7.90 (dm, J = 8.8 Hz, 2H), 11.71 (br s, 1H). Anal. Calcd for $C_{10}H_{12}N_2O_6S_2$: C, 37.49; H, 3.77; N, 8.74; S, 20.018. Found: C, 37.45; H, 3.72; N, 8.65; S, 20.05.

5c: ^{1}H NMR (250 MHz, DMSO-d_6): δ 4.09 (dd, J = 6.3, 8.5 Hz, 2H), 4.38 (dd, J = 7.2, 9.4 Hz, 2H), 7.38 (dm, J = 9.1 Hz, 2H), 8.24 (dm, J = 9.1 Hz, 2H), 11.90 (br s, 1H). Anal. Calcd for $C_9H_9N_3O_6S$: C, 37.63; H, 3.16; N, 14.63; S, 11.16. Found: C, 37.49; H, 3.08; N, 14.46; S, 11.09.

5d: ^{1}H NMR (250 MHz, DMSO-d_6): 3.93 (dd, J = 6.3, 8.5 Hz, 2H), 4.33 (dd, J = 6.3, 7.2 Hz, 2H), 7.21 (dm, J = 8.8 Hz, 2H), 7.43 (dm, J = 8.8 Hz, 2H), 11.19 (s, 1H). Anal. Calcd for $C_9H_9ClN_2O_4S$: EI-MS m/z (M^+) 275.9977, obsd 275.997156.

5e: ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.90 (dd, J = 6.0, 8.2 Hz, 2H), 4.29 (dd, J = 7.2, 8.5 Hz, 2H), 7.13−7.25 (m, 3H), 7.33−7.42 (m, 2H), 10.97 (br s, 1H). Anal. Calcd for $C_9H_{10}N_2O_4S$; C, 44.62; H, 4.16; N, 11.56. Found: C, 44.34; H, 4.18; N, 11.53.

5f: ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.62 (s, 3H), 3.94 (dd, J = 6.3, 8.2 Hz, 2H), 4.39 (dd, J = 6.3, 7.2 Hz, 2H), 8.12 (br s, 1H). Anal. Calcd for $C_4H_8N_2O_4S$: C, 26.66; H, 4.47; N, 15.54. Found: C, 26.73; H, 4.50; N, 15.54.

5g: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (t, J = 7.2 Hz, 6H), 3.46 (q, J = 7.2 Hz, 4H), 4.05 (dd, J = 7.6, 9.1 Hz, 2H), 4.40 (dd, J = 7.6, 9.1 Hz, 2H). Anal. Calcd for $C_7H_{14}N_2O_4S$: C, 37.83; H, 6.35; N, 12.60; S, 14.42. Found: C, 37.88; H, 6.29; N, 12.55; S, 14.49.

Typical Operating Procedure for Synthesis of Sulfamide 6b. A 100-L glass-lined reactor was charged with acetonitrile (17.8 kg) and 4-methylsulfonylaniline hydrochloride (3.36 kg, 16.2 mol) under stirring at room temperature. Triethylamine (4.5 kg, 44.47 mol) and 2-oxo-oxazolidine-3-sulfonic acid isopropylamide (**5h**) (3.70 kg, 17.77 mol, 1.1 equiv) were then added at the same temperature. The reaction mixture was heated to reflux and stirred at the same temperature for a minimum of 6 h. The solution was then slowly cooled to room temperature and kept agitated overnight. Water was slowly added over 40 min, and the reactor was placed under vacuum to distill as much as possible of acetonitrile (27.8 kg of distillate) while maintaining the reaction temperature below 40 °C. The suspension was cooled to room temperature and stirred for a minimum of 2 h before filtering the product. The cake was rinsed with water (16.2 kg) and dried under vacuum at about 50 °C for a minimum of 16 h to yield the 1-methylethylamino-1-sulfonic acid (4-methanesulfonylphenyl)amide (**6b**) (4.03 kg, 13.8 mol, 85%). Mp 165.5−167 °C. ^{1}H NMR (DMSO-d_6): δ 0.99 (d, J = 6.6 Hz, 6H), 3.16 (s, 3H), 3.33 (m, 1H), 7.30 (dm, J = 8.8 Hz, 2H), 7.76 (d, J = 7.9 Hz, 1H), 7.81 (dm, J = 8.8 Hz, 2H), 10.33 (br s, 1H).

6a: ^{1}H NMR (250 MHz, DMSO-d_6): δ 0.98 (d, J = 6.6 Hz, 6H), 2.23 (s, 3H), 3.21−3.44 (m, 1H), 6.96−7.13 (m, 4H), 7.22 (d, J = 7.2 Hz, 1H), 9.41 (s, 1H). Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.064; N, 12.27; S, 14.04. Found: C, 52.78; H, 7.06; N, 12.30; S, 14.17.

6c: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.13 (d, J = 6.6 Hz, 6H), 2.45 (s, 3H), 3.56 (m, J = 6.6, 7.6 Hz, 1H), 4.58 (d, J = 7.6 Hz, 1H), 6.93 (s, 1H), 7.11 (dm, J = 8.8 Hz, 2H), 7.23 (dm, J = 8.8 Hz, 2H). Anal. Calcd for $C_{10}H_{16}N_2O_2S_2$: EI-MS m/z (M^+) 260.0642, obsd 260.065322.

6d: ^{1}H NMR (250 MHz, DMSO-d_6): δ 0.99 (d, J = 6.6 Hz, 6H), 3.16−3.56 (m, 1H), 7.15 (dm, J = 9.0 Hz, 2H), 7.33 (dm, J = 9.0 Hz, 2H), 7.44 (d, J = 7.5 Hz, 1H), 9.77 (s, 1H). Anal. Calcd for $C_9H_{13}ClN_2O_2S$: C, 43.46; H, 5.27; N, 11.26; S, 12.89; Cl, 14.25. Found: C, 43.45; H, 5.20; N, 11.18; S, 12.59; Cl, 14.13.

6e: ^{1}H NMR (250 MHz, DMSO-d_6): δ 0.98 (d, J = 6.61 Hz, 6H), 3.21−3.51 (m, 1H), 6.97 (t, J = 7.1 Hz, 1H), 7.1 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.1 Hz, 2H), 7.32 (d, J = 8.5 Hz, 1H), 9.58 (s, 1H). Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.58; N, 13.07; S, 14.96. Found: C, 50.52; H, 6.52; N, 13.07; S, 15.11.

6f: ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.20 (s, 3H), 3.13 (s, 3H), 6.99 (dm, J = 8.5 Hz, 2H), 7.07 (dm, J = 8.5 Hz, 2H), 7.32 (dm, J = 8.8 Hz, 2H), 7.80 (m, J = 8.8 Hz, 2H), 10.34 (s, 1H), 10.77 (s, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: EI-MS m/z (M^+) 340.0553, obsd 340.055151.

6g: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 3H), 1.21 (d, J = 6.6 Hz, 6H), 1.30 (s, 6H), 1.59 (q, J = 7.4 Hz, 2H), 3.43−3.67 (m, J = 6.6 Hz, 1H), 4.27 (d, J = 7.6 Hz, 1H), 4.33 (s, 1H). Anal. Calcd for $C_8H_{20}N_2O_2S$: C, 46.12; H, 9.68; N, 13.45; S, 15.39. Found: C, 45.43; H, 9.67; N, 12.67; S, 15.02.

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