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A novel method for the synthesis of vicinal disulfonamides promoted by metallic samarium in aqueous media

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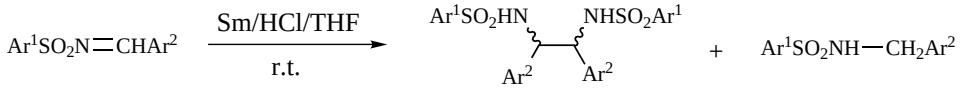
Abstract—A new method to synthesize vicinal disulfonamides by reductive coupling of *N*-sulfonylimines in Sm/HCl/THF has been developed and various reaction conditions have been studied.

Recently, growing interest has been focused on synthetic organic reactions in aqueous media. Water possesses many advantages over traditional organic solvents: simple operation, safety, low cost, the minimization of tedious protection and deprotection, etc. Many organic reactions have been successfully carried out in aqueous media, such as Diels–Alder reactions, Barbier reactions, Claisen rearrangements and aldol reactions.[1] Reactions in aqueous media promoted by a metal (such as In, Zn, Sn, etc.) have been extensively reported.[1a,2] Metallic samarium is stable in air and its reducing power ($Sm^{3+}/Sm = -2.41$ V) is similar to that of magnesium ($Mg^{2+}/Mg = -2.37$ V) and superior to that of zinc ($Zn^{2+}/Zn = -0.71$ V). However, the reactions promoted by samarium in aqueous media have been investigated less.[3,4]

On the other hand, compared with vicinal diamines, which are of interest due to their application in asymmetric synthesis[5] and medicinal chemistry[6] and which have been synthesized by various methods,[7] vicinal disulfonamides have rarely been studied.[8] Pansare reported that cyclic sulfamides can be synthesized via intramolecular coupling of dibenzylidine sulfamides promoted by Zn/TMSCl in DMF.[8] When performing cross coupling of *N*-sulfonylimines and aromatic ketones we found that SmI_2 could promote the dimerization of *N*-sulfonylimines to afford vicinal disulfonamides.[9] Here we report a convenient and practical method to synthesize vicinal disulfonamides via the reductive coupling of *N*-sulfonylimines promoted by metallic samarium in HCl/THF (Scheme 1).

Various activators and reaction media were studied to optimize the reaction conditions (Table 1). Our group has reported that saturated NH_4Cl can activate Sm.[10] However, Sm/NH_4Cl/THF does not provide vicinal disulfonamides without catalytic I_2 (entry a). Better yields were obtained by adding a catalytic amount of I_2 (entries b and c). Thus, we deduced that I_2 might have an important effect on the activation of Sm, so we used a catalytic amount of I_2 alone to perform the reductive coupling, however, only a trace amount of the product was obtained (entry d). When 2 equiv. of I_2 were used, the conversion of **1a** was nearly 100% but the chemoselectivity was poor (entries e and f). We also investigated the reaction promoted by Sm/Me_3SiCl and Sm/Me_2SiCl_2 in anhydrous THF and moderate yields of **2a**



1 **2** (*dl*/*meso*) (major) **3** (minor)

Scheme 1.

Keywords: vicinal disulfonamides; samarium reagents; aqueous media; reductive coupling.
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Table 1. The reductive coupling of *N*-sulfonylimine (**1a**, 1 mmol) under various conditions

Entry	Sm (mmol)	Reaction medium, additive	Reaction time	Yield (%)[a] of **2a**	Yield (%)[a] of **3a**
a	4	Satd. NH_4Cl/THF (5:1)	12 h	<5	<5
b	4	Satd. NH_4Cl/THF (5:1), I_2 (cat.)	12 h	37	7
c	4	Satd. NH_4Cl/THF (5:1), I_2 (cat.)	24 h	42	8
d	4	H_2O/THF (5:1), I_2 (10% mmol)	24 h	<2	<2
e	4	H_2O/THF (5:1), I_2 (2 mmol)	12 h	54	44
f	4	H_2O/THF (5:1), I_2 (2 mmol)	24 h	55	44
g	2	H_2O/THF (5:1), I_2 (1 mmol)	24 h	41	30
h	1.2	THF, Me_3SiCl (4 mmol)	15 h	73	10
i	1.2	THF, Me_2SiCl_2 (4 mmol)	10 h	76	8
j	4	1 HCl/THF (5:1)	30 min	85	9
k	4	1 HCl/EtOH (5:1)	30 min	83	9
l	4	2 HCl/THF (5:1)	30 min	74	18
m	4	0.1 HCl/THF (5:1)	30 min	75	8
n	4	1 M HCl/H_2O (5:1)	30 min	0	0
o	2	1 M HCl/THF (5:1)	30 min	63	4

[a] Isolated yields.

were obtained (entries h and i).[11] Finally we used hydrochloric acid to perform the reductive coupling of **1a** and obtained a satisfactory result (entry j). A certain amount of organic solvent is still necessary for the reductive coupling (entry n), both THF and EtOH are useful (entries j and k). The concentration of hydrochloric acid also influences the yields of the products, for example, 2 M HCl decreases the yield of **2a** but increases the yield of **3a** (entry l), and 0.1 M HCl reduces the yields of both **2a** and **3a** (entry m). Compared with the other methods mentioned above, the Sm/HCl/THF system needs a shorter reaction time and does not require the exclusion of oxygen.

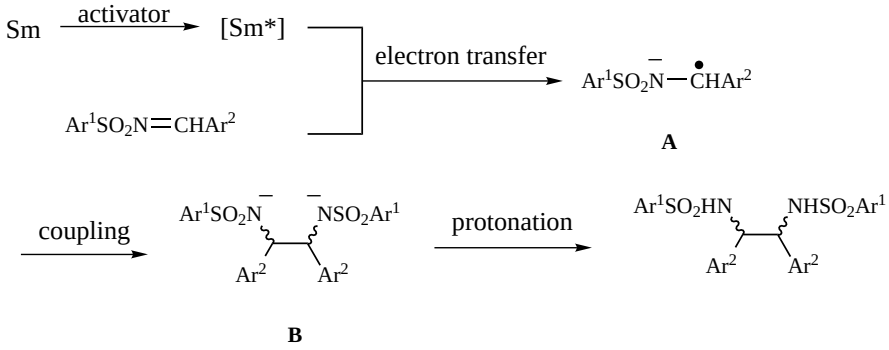
When 1 M hydrochloric acid was added dropwise to a suspension of Sm powder and the substrate in THF under air, hydrogen was released immediately and the reaction was completed within 30 min (Scheme 1). All the aromatic *N*-sulfonylimines (**1a**–**h**) investigated here give vicinal disulfonamides (**2a**–**h**) in good yields. The ratio of *dl*/*meso* is almost 1:1 (Table 2). Unlike aromatic *N*-sulfonylimines, the reactions of aliphatic *N*-sulfonylimines in Sm/HCl/THF gave exclusively the corresponding sulfonamides (**1i**–**k**) in quite low yields.

On the basis of previous work on reductive coupling reaction in Sm/HCl,[4a] a possible mechanism is postulated (Scheme 2). Perhaps the samarium powder is activated by the hydrochloric acid and an electron transfer to the substrate forms the radical anion (**A**), which then dimerizes and is protonated to afford the product **2a**, but the real nature of the reducing species [Sm*] in this system is unclear.[4a,12] The radical anion of the aliphatic *N*-sulfonylimines may be too unstable to dimerize and the reductive products formed exclusively. Similar to the Sm/I_2/H_2O/THF system, when satd. NH_4Cl/THF/I_2 (cat.) is used, a deep blue solution was observed, which turned yellow when the reaction was completed. However, in the absence of I_2 (10% mmol), we did not see a blue solution. Since divalent samarium shows a deep blue color, these phenomena suggest that I_2 might help to form the divalent samarium. In the

Table 2. The reductive coupling of *N*-sulfonylimines (**1a**–**h**)[14,15]

Entry	Ar^1 of **1**	Ar^2 (R) of **1**	Yield (%)[a]	Ratio of *dl*/*meso*[b]	Yield (%)
a	4-CH_3-C_6H_4	4-CH_3-C_6H_4	85 (**2a**)	51:49	9 (**3a**)
b	C_6H_5	4-CH_3-C_6H_4	80 (**2b**)	50:50	8 (**3b**)
c	4-CH_3-C_6H_4	C_6H_5	78 (**2c**)	45:55	6 (**3c**)
d	C_6H_5	4-CH_3O-C_6H_4	79 (**2d**)	48:52	10 (**3d**)
e	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	77 (**2e**)	50:50	12 (**3e**)
f	C_6H_5	4-Cl-C_6H_4	83 (**2f**)	46:54	4 (**3f**)
g	4-CH_3-C_6H_4	4-Cl-C_6H_4	85 (**2g**)	50:50	3 (**3g**)
h	4-CH_3-C_6H_4		72 (**2h**)	50:50	15 (**3h**)
i	4-CH_3-C_6H_4	$CH_3(CH_2)_3$	0	–	41 (**3i**)
j	4-CH_3-C_6H_4	$(CH_3)_2CHCH_2$	0	–	35 (**3j**)
k	4-CH_3-C_6H_4	$CH_3CH_2CH_2$	0	–	48 (**3k**)

[a] Isolated yields.
[b] The ratio of *dl*/*meso* was determined from the ^1H NMR spectra.



Scheme 2.

Sm/Me_3SiCl and Sm/Me_2SiCl_2 systems, we assumed that the mechanism is similar to that of pinacolic coupling promoted by Sm/Me_3SiCl.[11,13]

In summary, reductive coupling of *N*-sulfonylimines promoted by Sm/HCl/THF is a convenient and practical method to synthesize vicinal disulfonamides. This method adds to the reactions in aqueous media promoted by samarium reagents. Its advantages include no need for a nitrogen atmosphere, good yields, mild reaction conditions and simple operation.[14,15]

Acknowledgements

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14. General procedure: to a suspension of the substrate (1 mmol) and samarium powder (0.66 g, 4 mmol) in THF (2 mL) 1 M hydrochloric acid (10 mL) was added dropwise with stirring at room temperature. After the reaction was completed (monitored by TLC), the mixture was extracted by AcOEt (3×20 mL) and the AcOEt solution was washed with saturated NaCl (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by preparative TLC (cyclohexane–ethyl acetate (2:1) as eluent).
15. Typical physical data of compounds **2a (*N*-(2-(4-methyl)benzenesulfonylamino-1,2-di(4-methyl)phenylethyl)-4-methylbenzenesulfonamide)**: colourless crystals, mp 142–147°C; ν_{max}: 3277, 3030, 1595, 1495, 1323, 1159, cm^{-1}; ^1H NMR (400 MHz, DMSO): 8.00 (2H, d, NH), 7.14 (4H, d, ArH), 6.96 (4H, d, ArH), 6.74 (4H, d, ArH), 6.66 (4H, d, ArH), 4.48 (*dl*) and 4.45 (*meso*) (2H, s, CH), 2.24 (6H, s, $ArCH_3$), 2.11 (6H, s, $ArCH_3$); *m*/*z* (%): 393 (0.95), 274 (88.69), 155 (31.62), 91 (100), 77 (12.13). Anal. $C_{30}H_{32}N_2O_4S_2$. Calcd: C, 65.69; H, 5.84; N, 5.11; S, 11.68. Found C, 65.72; H, 5.86; N, 5.11; S, 11.65%.