Synthesis of Aromatic Aminosulfonic Acid Nitroamides

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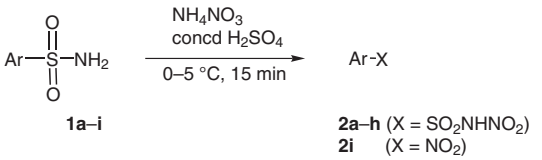
Abstract: Nitration of aromatic aminosulfonic acid primary amides to furnish the corresponding sulfononitroamides has been described for the first time. The conditions of nitration applied ensure chemoselective mononitration and prevent decomposition of the product. Synthesis of dabsyl nitroamide sodium salt, as a potential β-amyloid aggregation inhibitor is also reported.

Key words: sulfonamides, nitration, amines, arenes, azo compounds

Aromatic aminosulfonic acids have long been valuable reagents for organic synthesis, especially for dye and sulfadrug chemistry.[1] A number of alternative compounds with the acidic sulfonic group replaced by an activated sulfamoyl group such as acylsulfonamide,[1a,2] sulfonylchloramide,[3] sulfonylcyanamide,[4] sulfonylnitroguanidine,[4] sulfonylsulfonamide,[1a,5] and sulfonylcyanoguanidine[6] derivatives has been developed. Given a large number of already-known aromatic derivatives of sufonamides and over a century of experience with their nitration it seems striking that aromatic aminosulfonic acid nitroamides have been unknown till recently. Among N^1-acyl, cyano and sulfonyl sulfanilamide derivatives there are pharmaceuticals and leads for designing other valuable compounds,[7] which suggests also potential applications of the N^1-nitro derivative. Access to aromatic aminosulfonic acid nitroamides would diversify the set of relatively acidic carboxylic acid isosteres derived from sulfonic acid and consequently the construction of potentially biologically active compounds.[1a,b,6,7a] Furthermore, the synthesis of the title nitroamides would provide a novel approach to the modification of sulfamoyl substituent of aromatic aminosulfonic acid amides.

Two methods for the N-nitration of primary aromatic sulfonamides have been reported so far. The first employs concentrated HNO_3 as a nitrating agent and this method has not been extended beyond benzenesulfonamide and *p*-toluenesulfonamide.[8] Reports on this method pointed out preparative difficulties due to the product instability in strong acidic media, extreme solubility in water and also possible double nitration. The second method, which avoids the difficulties, utilises NO_2BF_4 as a nitrating agent. Although this method is complicated, because it requires anhydrous conditions and involves operations with NH_3 and HCl gases, yet it opens an access to sulfononitroamides bearing alkoxy, carboxy, halogen or nitro substituents in the benzene ring.[9] Another approach, specific for preparation of *N*-nitro-2-sulfamoylbenzoic acid esters, follows nitration of saccharin and subsequent solvolysis of its nitroimide.[10] The known procedures of the nitration of aromatic aminosulfonic acid primary amides report decomposition of the nitroamide intermediate[11] or introduction of the nitro substituent into the aromatic system[12] but none of them reports on isolation of the corresponding nitroamide.

In strongly acidic conditions, the protonated amino group of aromatic aminosulfonamides deactivates the aromatic amino moiety against nitration. It does not happen in the second method due to the low acidity of the medium.[13] Moreover, as for the sulfanilic acid, the *N*-nitrosulfamoyl acidic group that is present in aromatic amine should be able to protonate the basic centre and form a zwitterionic, easy to isolate product. For these reasons the former method, an age-old nitration in concentrated H_2SO_4 with some modifications was adopted. In fact, as anticipated earlier, nitration of selected sulfonamides in concentrated H_2SO_4 at 0–5 °C over a 15-minute period yielded the corresponding nitroamides (Scheme 1, Table 1).



Scheme 1 Chemoselective nitration of sulfonamides **1a–i**

For convenience, concentrated HNO_3 originally used as a nitrating agent was replaced with solid NH_4NO_3, which was added to the cold solution of sulfonamide in concentrated H_2SO_4. It is worth mentioning that pouring the reaction mixture onto ice resulted in the separation of pure solid product (**2b**, **2d–h**; >95% purity by ^{1}H NMR spectroscopic analysis). Only **2a** and **2c** were contaminated with side products (85 and 92% purity by ^{1}H NMR analysis respectively). In the latter case, there was only one side product, 4-sulfobenzylamine (**3**).[14] Unlike all aromatic sulfonic acid nitroamides, the products **2a–h** were soluble only in bases and some polar aprotic solvents. Therefore, in contrast to the original procedure, the diethyl ether extraction could have been omitted, and water processing turned out to be suitable for the product. Up to this point the above mentioned isolation had matched the one corresponding to *N*-alkylbenzenesulfo-*N*-nitroamides.[15a] How-

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Table 1 Chemoselective Nitration of Aromatic Aminosulfonamides with NH_4NO_3 in Concentrated H_2SO_4

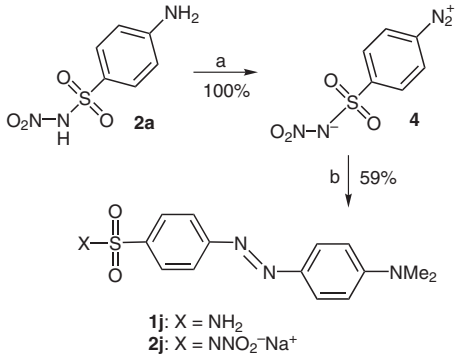
$ArSO_2NH_2$	Product	Yield (%)[a]
1a (Ar = 4-$H_2NC_6H_4$)	**2a**	50
1b (Ar = 4-$Me_2NC_6H_4$)	**2b**	84
1c (Ar = 4-$H_2NCH_2C_6H_4$)	**2c**	73[b]
1d (Ar = 3-H_2N-4-MeC_6H_3)	**2d**	96
1e (Ar = 3-H_2N-4-ClC_6H_3)	**2e**	71
1f (Ar = 2-$H_2NC_6H_4$)	**2f**	79
1g (Ar = 5-$Me_2NC_{10}H_6$)[c]	**2g**	71
1h (Ar = 3-pyridyl)	**2h**	62
1i (Ar = 4-H_2N-3,5-$Cl_2C_6H_2$)	**2i**	21[d]

[a] Isolated yield of analytically pure (^{1}H NMR, ^{13}C NMR and elemental analysis or HRMS) nitro product, except for **2c** and **2i**.
[b] Product contains 8% of 4-sulfobenzylamine (**3**).[14] This mixture was converted into **3**. The identity and the yield of products were established on the basis of NMR and MS comparison of the isolated product mixture and pure **3**. The result was the same, when hydrochloride of **1c** was nitrated.
[c] 5-Dimethylamino-1-naphthalenesulfonamide.
[d] Isolated yield after modified work-up procedure.[16]

ever, even the latter could not be applied as it was, because solvents recommended for their crystallisation turned out to be useless. Typically, nitration was conducted on a 3.3 mmol scale. However, for sulfanilamide (**1a**), it was scaled up ten times successfully, with only slight loss of the product purity (81% by ^{1}H NMR analysis). Extension of the reaction time or running the reaction at room temperature resulted in a decreased yield and purity of **2a**. The procedure applied for **1i** yielded product of the desulfonation–nitration **2i** and the recovered substrate.

Some properties of **2a** could be representative for all products in the series **2a**–**h**. Thus, **2a** is a solid, which rapidly decomposes without melting at >200 °C. It is soluble in aqueous alkali and ammonia, DMSO, DMF and pyridine. Taking into account, that the NO_2 group is more electron-withdrawing than CN, **2a** should be a stronger acid than N^1-cyanosulfanilamide ($pK_a = 2.92$).[17] As in the latter case, evidence for the formation of zwitterion was found in the solid state: the IR spectrum (KBr) of **2a** reveals strong and broad absorption with several sub-maxima in the 3250–2000 cm^{-1} region and the lack of absorption above this region. High lability of its acidic protons was reflected in the ^{1}H NMR spectra, where their signals were located with the signals of residual water contained in DMSO-d_6.

To enrich the set of the prepared nitroamides and their synthetic usefulness, a synthesis of a *N*-nitro phenylazobenzenesulfonamide analogue **2j** of the potent β-amyloid aggregation inhibitor, dabsyl amide **1j**[1b] was attempted (Scheme 2). This time however, the nitration procedure applied for the latter failed. A mixture of products was formed with a trace amount of the desired compound **2j** (by ^{1}H NMR). Cleavage of diazo compounds under nitration conditions has been already reported.[18] Another attempted approach, diazotisation of **2a** and coupling of betaine **4** with *N*,*N*-dimethylaniline, was successful, affording **2j** with 59% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) aq Na_2CO_3, then aq $NaNO_2$, HCl; 0 °C; (b) *N*,*N*-dimethylaniline, AcOH then aq NaOH.

Previous reports on the reactivity of aromatic sulfonic acid nitroamides usually describe transformations of the amide group.[15] The above-presented synthesis is a rare modification leaving the amide group intact.[8b,19] Thus, the synthesis of an analogue of the biologically active aminosulfonic acid derivative containing sulfononitroamide carboxylic acid isostere has been demonstrated for the first time.

In summary, selective nitration of structurally diverse aromatic aminosulfonic acid primary amides **1a**–**j** led in a simple way to novel nitroamides **2a**–**h**. The formation and coupling of diazonium betaine **4** was illustrated with preparation of novel *N*-nitrophenylazo benzenesulfonamide derivative **2j**, as a potential β-amyloid aggregation inhibitor.

CAUTION! Solid diazonium betaine **4** explodes upon heating to its melting point.[20] Heating of nitroamide derivatives **2a**–**h**,**j** and exothermicity during nitration presented no serious issue. Nevertheless, because some compounds of this group belong to energetic materials and explosives, precautions should be taken when handling them. All starting compounds are known (**1b**,[21] **1d**,[22] **1e**,[22] **1h**[23] and **1j**[1b]) or commercially available (**1a**, **1c** hydrochloride, **1f**,**g** and **1i**). Analytical TLC was performed on Merck aluminum TLC plates (silica gel 60 F_{254}) with detection by UV light. Silica gel 60 (Merck 230–400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were HPLC grade. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer in DMSO-d_6 with TMS as an internal standard. NMR chemical shifts are given in ppm. MS spectra (EI) were obtained on AMD 402 BRD spectrometer operating at 70 eV. ESIMS spectra were measured on Waters Micromass® ZQ spectrometer.

N-Nitration of Aromatic Aminosulfonic Acid Amides; General Procedure

To a stirred solution of aromatic sulfonamide (3.3 mmol) in 95% H_2SO_4 (2.5 mL), was added NH_4NO_3 (268 mg, 3.35 mmol) over 5 min period at 0–5 °C and stirring was continued for additional 10

min at this temperature. The mixture was then poured onto ice to form a precipitate. The product was filtered, washed with H_2O (10 mL), and dried in vacuo over P_2O_5.[16] Additionally **2a** was recrystallised from H_2O and **2b** from MeCN, respectively, giving samples with correct elemental analyses.

N^1-Nitrosulfanilamide (2a)
^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.14 (d, J = 8.8 Hz, 2 H, H-3,5), 7.73 (d, J = 8.8 Hz, 2 H, H-2,6).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 119.36, 129.74, 136.74, 140.59.

Anal. Calcd for $C_6H_7N_3O_4S$: C, 33.18; H, 3.26; N, 19.34; S, 14.76. Found: C, 32.98; H, 3.29; N, 19.35; S, 14.71.

4-Dimethylamino-*N*-nitrobenzenesulfonamide (2b)
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.98 (s, 6 H, CH_3), 6.77 (d, J = 9.1 Hz, 2 H, H-3,5), 7.58 (d, J = 9.1 Hz, 2 H, H-2,6).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 40.53, 111.65, 128.17, 129.65, 151.25.

Anal. Calcd for $C_8H_{11}N_3O_4S$: C, 39.18; H, 4.52; N, 17.13; S, 13.07. Found: C, 39.18; H, 4.54; N, 17.03; S, 13.11.

4-Aminomethyl-N^1-nitrobenzenesulfonamide (2c)
This product was contaminated with 8% of **3**.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.1 (q, J = 5.7 Hz, 2 H, CH_2), 7.55 (d, J = 8.5 Hz, 2 H, H-3,5), 7.81 (d, J = 8.5 Hz, 2 H, H-2,6), 8.16 (br s, 3 H, NH_3^+).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.93, 128.12, 128.62, 137.18, 142.60.

ESIMS (negative ion): m/z (%) = 230 (100, M – H^+), 186 (30, M – N_2O – H^+), 120 (10).

3-Amino-4-methyl-N^1-nitrobenzenesulfonamide (2d)
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (s, 3 H, CH_3), 7.43 (d, J = 8.3 Hz, 1 H, H-5), 7.62 (dd, J = 7.9, 1.8 Hz, 1 H, H-6), 7.77 (d, J = 1.9 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.01, 121.95, 126.31, 130.99, 131.55, 134.49, 141.15.

HRMS: m/z [M]$^+$ calcd for $C_7H_9N_3O_4S$: 231.0314; found: 231.0337.

3-Amino-4-chloro-N^1-nitrobenzenesulfonamide (2e)
^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.00 (dd, J = 8.4, 2.2 Hz, 1 H, H-6), 7.34 (d, J = 2.2 Hz, 1 H, H-2) overlapped with 7.34 (d, J = 8.4 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 115.77, 117.40, 121.06, 128.94, 142.04, 142.46.

HRMS: m/z [M]$^+$ calcd for $C_6H_6ClN_3O_4S$: 250.9768; found: 250.9778.

2-Amino-N^1-nitrobenzenesulfonamide (2f)
^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.03 (ddd, J = 8.0, 8.1, 1.1 Hz, 1 H, H-5) overlapped with 7.04 (dd, J = 7.1, 1.0 Hz, 1 H, H-3), 7.41 (ddd, J = 8.1, 7.1, 1.4 Hz, 1 H, H-4), 7.68 (dd, J = 8.1, 1.5 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 120.16, 121.17, 127.97, 130.54, 132.98, 139.23.

HRMS: m/z [M]$^+$ calcd for $C_6H_7N_3O_4S$: 217.0157; found: 217.0165.

***N*-Nitrodansylamide (2g)**
^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.15 (s, 6 H, CH_3), 7.64–7.82 (m, 2 H_{arom}), 7.77 (dd, J = 8.4, 7.5 Hz, 1 H_{arom}), 8.25 (dd, J = 7.5, 0.8 Hz, 1 H_{arom}), 8.42 (d, J = 8.5 Hz, 1 H_{arom}), 8.6–8.7 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.35, 117.86, 125.61, 125.69, 126.33, 126.75, 129.33, 130.09, 139.37, 142.49.

HRMS: m/z [M]$^+$ calcd for $C_{12}H_{13}N_3O_4S$: 295.0627; found: 295.0628.

***N*-Nitro-3-pyridinesulfonamide (2h)**
^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.85 (dd, J = 8.0, 5.2 Hz, 1 H, H-5), 8.5 (dt, J = 8.0, 1.8 Hz, 1 H, H-6), 8.86 (dd, J = 5.2, 1.4 Hz, 1 H, H-4), 9.09 (d, J = 1.7 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 125.58, 139.43, 139.66, 146.68, 150.21.

HRMS: m/z [M]$^+$ calcd for $C_5H_5N_3O_4S$: 203.0001; found: 202.999.

Sodium 4-[4-(Dimethylamino)phenylazo]benzenesulfamoylnitronate (2j)
The scaled down procedure for methyl orange synthesis was adopted with some modifications.[24] The crude **2a** (81% pure, 1.08 g, 4.05 mmol) was used instead of sulfanilic acid. Acid form of **2j** was filtered, washed with H_2O (20 mL), suspended in aq 1 M NaOH (34 mL) and warmed at 70–80 °C until the suspension had been dissolved. Crystalline product separated as the solution cooled. The solid obtained was filtered, recrystallised from H_2O, and dried in a vacuum oven at 156 °C for 3 h over P_2O_5; yield: 888 mg (59%); reddish-orange crystals.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.08 (6 H, s, CH_3), 6.85 (d, J = 9.1 Hz, 2 H, XX′ from $C_6H_4SO_2$), 7.79–7.93 (6 H, m, AA′BB′ from $Me_2NC_6H_4$ overlapped with AA′ from $C_6H_4SO_2$).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 39.91, 111.53, 121.26, 125.20, 128.95, 142.34, 142.51, 152. 84, 153.84.

Anal. Calcd for $C_{14}H_{16}N_5NaO_5S$: C, 45.28; H, 3.80; N, 18.86; S, 8.63. Found: C, 45.29; H, 3.98; N, 18.82; S, 8.59.

4-Benzenediazoniumsulfamoylnitronate (4)
When the preparation of **2j** was stopped just after the diazotisation stage by pouring the reaction mixture into cold H_2O, the precipitate of **4** was isolated quantitatively as described earlier for nitroamides; mp 119 °C (exploded).

IR (KBr): 2302 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.31 (d, J = 9.0 Hz, 2 H_{arom}), 8.79 (d, J = 9.2 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 118.42, 129.61, 133.0, 153.14.

4-Sulfobenzylamine (3)[14]
To the cooled 95% H_2SO_4 (1 mL), was added crude **2c** (125 mg, 0.5 mmol) portionwise, and the resulting suspension was stirred continuously and allowed to warm to r.t. After the suspension had dissolved, the mixture was stirred for 30 min at r.t. N_2O had then stopped evolving and the mixture was poured onto ice. The solid obtained was filtered, washed with H_2O (5 mL) and dried; yield: 56 mg (60%).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.03, 125.78, 128.24, 133.95, 148.65.

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(16) In the modified procedure for the isolation of **2i**, the reaction mixture after pouring onto ice was extracted with EtOAc (4 × 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel, a hexane–EtOAc gradient solvent from 10:1 to 1:1) to give **2i** followed by recovered **1i**. Analytical data of the product **2i** (mp, R_f, ^1H and ^{13}C NMR) were consistent with a commercial sample of 2,6-dichloro-4-nitroaniline.

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