(Arylsulfonyl)acetones and -acetonitriles: New Activated Methylenic Building Blocks for Synthesis of 1,2,3-Triazoles

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Abstract: β-Keto sulfones and β-nitrile sulfones were used as building blocks for 1,2,3-triazole synthesis in the Dimroth cyclization. It was shown, that sulfone reagents undergo base-catalyzed cyclization under mild conditions (at room temperature) to give 1,2,3-triazoles in moderate to excellent yields. This fact has confirmed the high nucleophilicity of sulfonylmethylenic compounds and allows new synthetic applications.

Key words: azides, triazoles, sulfones, Dimroth reaction

Synthetic strategies that provide rapid and efficient library generation are of increasing importance.[1] In the current work we report the synthesis of aryl hetaryl sulfones. Such compounds are very attractive targets for the study of biological activity, as a few of them are anti-HIV agents. Following the discovery of 2-nitrophenyl phenyl sulfone (NNPS),[2,3] as a non-nucleoside inhibitor of HIV-1 reverse transcriptase, several articles have been dedicated to the synthesis of compounds of this class. For example, new derivatives, such as L-737126 and aryl 1*H*-pyrrol-1-yl sulfones (PASs), have been synthesized by substitution of the nitrophenyl moiety for 2-carbamoyl-5-chloro-1*H*-indol-3-yl or pyrrol-1-yl fragments (Figure 1). Subsequently, optimization of the indole-containing compound L-737126 has led to potent inhibitors[4] with equivalent anti-HIV-1 reverse transcriptase activity, but improved physicochemical properties.

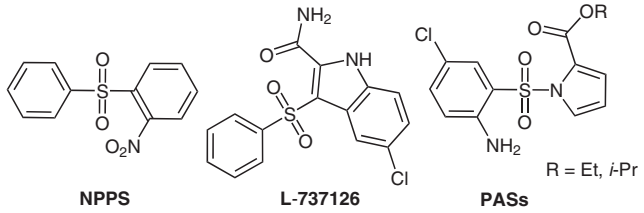

Figure 1 Aryl sulfones anti-HIV agents

The importance of the diaryl sulfone moiety for the design of new potential anti-HIV-1 agents is confirmed by studies of novel aryl pyrrolyl sulfones and related indole sulfones.[5–7] Recently, three-dimensional quantitative structure–activity relationship (3-D QSAR) studies and docking simulations have been developed on aryl indolyl sulfones.[8] Efforts in the direction of anti-HIV-1 agents have led us to the design of 1,2,3-triazole derivatives with an aryl sulfone fragment.

It is well known, that organic azides undergo base-catalyzed condensation reactions with activated methylenic compounds.[9] Stabilized and nonstabilized carbanions react with organic azides to form triazenyl anions, which can then be trapped regioselectively with electrophiles under appropriate reaction conditions. The triazenyl anions that are formed in the presence of an internal electrophile undergo ring closure to give triazoles (Dimroth reaction).[10] Malonic, cyanoacetic, and related esters can be used as substrates. Furthermore, in β-keto sulfones or β-nitrile sulfones the internal electrophile can be a carbonyl or cyano group. Moreover, the sulfonyl azides are used for diazo transfer to CH-acid compounds, especially for activated β-keto esters and β-keto sulfones.[11,12] In this case, the enolate or enol attacks the organic azide with formation of a triazene, which reacts after tautomerization and forms the diazo compound and the sulfonamide.

Herein, azides and sulfones were used as starting materials for the synthesis of 1,2,3-triazoles, prepared from commercially available aromatic amines. Diazotization of anilines **1a–g** with sodium nitrite and followed by reaction with sodium azide led to aryl azides **3a–e** in 67–83% yields. The reaction of diazonium salts **2a–c**,**e** with sulfur dioxide in acetone gave arenesulfonyl chlorides **4a–d** in 79–91% yields. Reduction of compounds **4a–d** with zinc gave sodium sulfinates **5a–d** and their subsequent reaction with one equivalent of chloromethylenic compounds **6a**,**b** yielded the corresponding β-keto sulfones **7a–d** or β-nitrile sulfone **7e**. Finally, reaction of sulfones **7a–e** with aryl azides **3a–e** occurred to yield triazoles **8a–l** (Scheme 1).

It was established that cyclization of azides **3** with sulfones **7** was rapid at room temperature or within a short reaction time after heating and gave triazoles **8a–l** in good yields without formation of byproducts (Table 1). Compounds **8a–c**,**e–g**,**i–l** were precipitated from methanol solution and were obtained with satisfactory purity. In the case of compounds **8d**,**h**, the initial product was heated with alkaline water leading to ester hydrolysis and then the carboxylic was acid crystallized.

A new synthesis of aryl 1*H*-1,2,3-triazol-4-yl sulfones has been developed. It was shown, that β-keto sulfones or β-nitrile sulfones are useful building blocks for the synthesis of heterocyclic products. Thus, the approach proposed can

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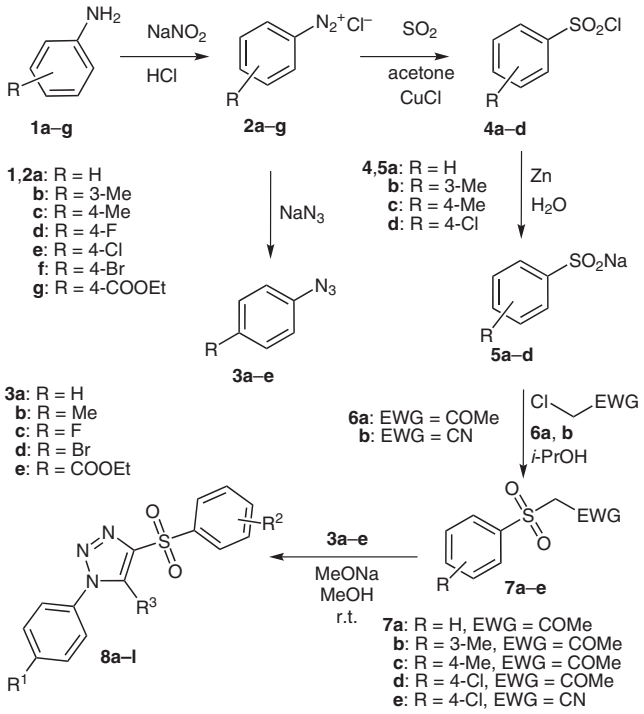

Scheme 1 A synthetic route to aryl 1*H*-1,2,3-triazol-4-yl sulfones **8a–l**

Table 1 Aryl 1*H*-1,2,3-Triazol-4-yl Sulfones **8a–l**

Triazole	R^1	R^2	R^3	Yield[a] (%)
8a	H	H	Me	70
8b	Me	H	Me	63
8c	Br	H	Me	75
8d	CO_2H	H	Me	81
8e	H	4-Me	Me	67
8f	Me	4-Me	Me	86
8g	Br	4-Me	Me	91
8h	CO_2H	4-Me	Me	74
8i	H	3-Me	Me	61
8j	H	4-Cl	Me	83
8k	H	4-Cl	NH_2	54
8l	F	4-Cl	NH_2	71

[a] Isolated yields are based on a single experiment and the yields were not optimized.

be used for the creation of compound libraries for biological activity testing.

All melting points were determined in capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H) with the deuterated solvent as the internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. The evolution of the reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates. Starting azides **3a–e**[13] and sulfonyl chlorides **4a–d**[14] were prepared from commercially available amines **1a–g** according to the procedures described in the literature. The sodium sulfinates **5a–d**, β-keto sulfones **7a–d**, and β-nitrile sulfone **7e** were prepared following the two-step literature procedure.[15,16]

4-(Arylsulfonyl)-1*H*-1,2,3-triazoles 8a–l; General Procedure

To a soln of MeONa (540 mg, 10.0 mmol) in anhyd MeOH (20 mL) was added substituted sulfone **7** (10.0 mmol). To this soln the appropriated aryl azide **3** (10.0 mmol) in anhyd MeOH (2 mL) was added dropwise and the solid started to precipitate. The mixture was stirred for several hours (r.t. for 2–5 h) until completion. The resulting suspension was filtered and the solid product was washed with MeOH to give the corresponding aryl 1*H*-1,2,3-triazol-4-yl sulfones **8a–c**,**e–g**,**i–l**.

For extraction of compounds **8d**,**h**, to the resulting suspension was added hot H_2O (20 mL) and a soln of NaOH to pH 11–12. The mixture was heated under reflux for 1 h. The hot soln was poured into concd HCl (10 mL) and left crystallize. The obtained solid was filtered, washed with H_2O (2 ×) and recrystallized (MeOH).

5-Methyl-1-phenyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazole (8a)

White crystals; yield: 70%; mp 165–166 °C (MeOH).

^{1}H NMR: δ = 2.59 (s, 3 H, CH_3), 7.58–7.74 (m, 8 H_{Ph}), 8.04 (d, *J* = 8.4 Hz, 2 H_{Ph}).

MS (CI): *m*/*z* (%) = 300 (100, $[M + 1]^+$).

Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.09; H, 4.45; N, 13.91.

5-Methyl-1-(4-methylphenyl)-4-(phenylsulfonyl)-1*H*-1,2,3-triazole (8b)

White crystals; yield: 63%; mp 134–135 °C (MeOH).

^{1}H NMR: δ = 2.45 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 7.39 (d, *J* = 8.4 Hz, 2 H, H_{Ar}-3,5), 7.44 (d, *J* = 8.4 Hz, 2 H, H_{Ar}-2,6), 7.64 (t, *J* = 7.2 Hz, 2 H, H_{Ph}-3,5), 7.71 (t, *J* = 7.2 Hz, 1 H, H_{Ph}-4), 8.02 (d, *J* = 7.2 Hz, 2 H, H_{Ph}-2,6).

MS (CI): *m*/*z* (%) = 314 (100, $[M + 1]^+$).

Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.46; H, 4.73; N, 13.59.

1-(4-Bromophenyl)-5-methyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazole (8c)

White crystals; yield: 75%; mp 154–155 °C (MeOH).

^{1}H NMR: δ = 2.58 (s, 3 H, CH_3), 7.58 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-3,5), 7.64 (t, *J* = 7.2 Hz, 2 H, H_{Ph}-3,5), 7.71 (t, *J* = 7.2 Hz, 1 H, H_{Ph}-4), 7.76 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-2,6), 8.03 (d, *J* = 7.2 Hz, 2 H, H_{Ph}-2,6).

MS (CI): *m*/*z* (%) = 378 (82, $[M + 1]^+$), 380 (100, $[M + 1]^+$).

Anal. Calcd for $C_{15}H_{12}BrN_3O_2S$: C, 47.63; H, 3.20; N, 11.11. Found: C, 47.48; H, 3.01; N, 11.02.

4-[5-Methyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazol-1-yl]benzoic Acid (8d)

White crystals; yield: 81%; mp 247–248 °C (MeOH).

^{1}H NMR: δ = 2.62 (s, 3 H, HH_3), 7.62–7.69 (m, 3 H, H_{Ph}-3,4,5), 7.72 (d, *J* = 8.4 Hz, 2 H, H_{Ar}-3,5), 8.03 (d, *J* = 7.2, 2 H, H_{Ph}-2,6), 8.16 (d, *J* = 8.4 Hz, 2 H, H_{Ar}-2,6), 13.10 (br s, 1 H, CO_2H).

MS (CI): *m*/*z* (%) = 343 (100, $[M^+]$).

Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 55.80; H, 3.61; N, 12.30.

5-Methyl-4-[(4-methylphenyl)sulfonyl]-1-phenyl-1*H*-1,2,3-triazole (8e)
White crystals; yield: 67%; mp 157–158 °C (MeOH).

^{1}H NMR: δ = 2.44 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 7.44 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-3,5), 7.56–7.64 (m, 5 H_{Ph}), 7.90 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 314 (100, $[M + 1]^+$).

Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.62; H, 4.82; N, 13.41. Found: C, 61.74; H, 4.61; N, 13.45.

5-Methyl-1-(4-methylphenyl)-4-[(4-methylphenyl)sulfonyl]-1*H*-1,2,3-triazole (8f)
White crystals; yield: 86%; mp 140–141 °C (MeOH).

^{1}H NMR: δ = 2.43 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 7.37–7.48 (m, 6 H_{Ar}), 7.90 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 328 (100, $[M + 1]^+$).

Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.28; H, 5.14; N, 12.99.

1-(4-Bromophenyl)-5-methyl-4-[(4-methylphenyl)sulfonyl]-1*H*-1,2,3-triazole (8g)
White crystals; yield: 91%; mp 151–152 °C (MeOH).

^{1}H NMR: δ = 2.44 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 7.44 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-3,5), 7.58 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 2 H, H_{Ar}-3,5), 7.78 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 2 H, H_{Ar}-2,6), 7.90 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 392 (80, $[M + 1]^+$), 394 (100, $[M + 1]^+$).

Anal. Calcd for $C_{16}H_{14}BrN_3O_2S$: C, 48.99; H, 3.60; N, 10.71. Found: C, 49.07; H, 3.76; N, 10.54.

4-{5-Methyl-4-[(4-methylphenyl)sulfonyl]-1*H*-1,2,3-triazol-1-yl}benzoic Acid (8h)
White crystals; yield: 74%; mp 209–210 °C (MeOH).

^{1}H NMR: δ = 2.45 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 7.44 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-3,5), 7.76 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-3,5), 7.91 (d, *J* = 8.0 Hz, 2 H, H_{Ar}-2,6), 8.19 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 357 (100, $[M^+]$).

Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.17; H, 4.14; N, 11.60.

5-Methyl-4-[(3-methylphenyl)sulfonyl]-1-phenyl-1*H*-1,2,3-triazole (8i)
White crystals; yield: 61%; mp 157–158 °C (MeOH).

^{1}H NMR: δ = 2.47 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 7.51–7.54 (m, 2 H_{Ar}), 7.58–7.65 (m, 5 H_{Ar}), 7.81–7.85 (m, 2 H_{Ar}).

MS (CI): *m*/*z* (%) = 314 (100, $[M + 1]^+$).

Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.18; H, 4.73; N, 13.55.

4-[(4-Chlorophenyl)sulfonyl]-5-methyl-1-phenyl-1*H*-1,2,3-triazole (8j)
White crystals; yield: 83%; mp 125–126 °C (MeOH).

^{1}H NMR: δ = 2.58 (s, 3 H, CH_3), 7.58–7.64 (m, 5 H_{Ph}), 7.68 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-3,5), 8.05 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 334 (100, $[M + 1]^+$).

Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59. Found: C, 54.14; H, 3.52; N, 12.45.

4-[(4-Chlorophenyl)sulfonyl]-1-phenyl-1*H*-1,2,3-triazol-5-amine (8k)
White crystals; yield: 54%; mp 164–165 °C (MeOH).

^{1}H NMR: δ = 6.55 (s, 2 H, NH_2), 7.50–7.62 (m, 5 H_{Ph}), 7.63 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-3,5), 8.03 (d, *J* = 8.8 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 335 (100, $[M + 1]^+$).

Anal. Calcd for $C_{14}H_{11}ClN_4O_2S$: C, 50.23; H, 3.31; N, 16.74. Found: C, 50.06; H, 3.23; N, 16.88.

4-[(4-Chlorophenyl)sulfonyl]-1-(4-fluorophenyl)-1*H*-1,2,3-triazol-5-amine (8l)
White crystals; yield: 71%; mp 182–183 °C (MeOH).

^{1}H NMR: δ = 6.56 (s, 2 H, NH_2), 7.34 (t, ^3J = 8.8 Hz, 2 H, H_{Ar}-3,5), 7.56 (dd, ^3J = 8.8 Hz, ^4J = 4.8 Hz, 2 H, H_{Ar}-2,6), 7.62 (d, ^3J = 8.8 Hz, 2 H, H_{Ar}-3,5), 8.02 (d, ^3J = 8.8 Hz, 2 H, H_{Ar}-2,6).

MS (CI): *m*/*z* (%) = 353 (100, $[M + 1]^+$).

Anal. Calcd for $C_{14}H_{10}ClFN_4O_2S$: C, 47.67; H, 2.86; N, 15.88. Found: C, 47.52; H, 2.69; N, 15.64.

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