Efficient One-pot Synthesis of 4-Ethynylbenzenesulfonamides

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One-pot simultaneous debrominative decarboxylation and sulfamation of anti-2,3-dibromo-3-(4-chlorosulfonylphenyl)propanoic acid in DMF (for alkylamines) or DMF-pyridine (1/1, for arylamines) using a diverse range of alkyl and aryl amines under microwave irradiation stereoselectively afforded intermediate (Z)-4-(2-bromovinyl)benzenesulfonamides. The intermediates, without isolation and purification, were treated with EtONa to give the desired 4-ethynylbenzenesulfonamides.

Key words: One-pot Synthesis, Arenesulfonamide, Arylacetylene, Amine, Microwave Irradiation

Introduction

Arenesulfonamides have long been the subject of pharmaceutical interest due to their biological activities [1]. They are used in the prevention and treatment of bacterial infections, diabetes mellitus, oedema, hypertension, and gout. Some of them have proved to be useful as herbicides [2] and plaguescides [3]. Arenesulfonamides can be converted to a number of other important compounds such as acylsulfonamides [4]. Arenesulfonamide derivatives of azo dyes have been reported to improve light stability and fibre fixation [5].

Arylacetylenes are also useful and versatile intermediates in organic synthesis. Their use as precursors for the synthesis of oligo(arylenealkyne) macrocycles [6] has stimulated a great deal of interest in their synthesis. More recently, benzenesulfonamides containing a 4-ethynyl substituent were frequently utilized in click chemistry for the preparations of novel carbonic anhydrase inhibitors [7]. However, expensive transition metal catalysts such as Pd(PPh 3) 4 and alkyn reagents were needed in the presently used synthetic method [8], which involves the coupling reaction between 4-bromobenzene sulfonamide and ethynyltri-methylsilane followed by deprotection.

Microwave-induced rate-accelerating technology is becoming a powerful tool in organic synthesis. Our previous study showed that microwave irradiation of anti-2,3-dibromoalkanoic acids in DMF in the presence of triethylamine for 0.2 – 1.0 min stereoselectively afforded (Z)-vinyl bromides in nearly quantitative yields [9]. We found recently that (Z)-aryl-vinyl bromides could be converted into the corresponding arylacetylene in the presence of DBU in high yields [10].

In this paper, we report a facile one-pot method for the synthesis of 4-ethynylbenzenesulfonamides 3 from anti-2,3-dibromo-3-(4-chlorosulfonylphenyl)propanoic acid (1) and various amines 2 (Scheme 1).

Results and Discussion

Microwave irradiation of a solution of 1 and 2 in DMF (for alkylamines) or DMF-pyridine (1/1, for arylamines) stereoselectively afforded intermediate (Z)-4-(2-bromovinyl)benzenesulfonamides 3. Assignment of the configuration of (Z)- and (E)-arylviny bromides was made on the basis of 1H NMR spectra. The 1H NMR spectrum of Ar-CH=CH=Br exhibits an AA’BB’-type pattern. Particularly, (Z) and (E) vicinal
coupling constants are $J_Z = 8.0 – 8.5$ Hz and $J_E = 13.9 – 14.5$ Hz, respectively. The intermediates 3, without isolation and purification, were treated with EtONa at $60 \degree C$ for 2 h to give the desired 4-ethynylbenzenesulfonamides 4. It is noteworthy that amines 2, in our procedure, were used not only as reactants but also as bases instead of triethylamine for the selective conversion of 1 to the intermediate 3. To the best of our knowledge, the use of various amines for the selective conversion of 1 to (Z)-aryvinyl bromides has not been reported. The one-pot synthetic method is convenient in comparison with a two-step strategy because compounds 4 could be obtained directly from 1 without the isolation of 3. Compound 1 was easily prepared by bromination of trans-4-chlorosulfonyl-cinnamic acid in HOAc.

Cyclohexylamine (2a) was used firstly as a model substrate for alkylamines. Intermediate 3a was obtained by simultaneous debrominative decarboxylation and sulfamation of 1 and 2a in DMF under microwave condition for 25 s. Treatment of the reaction mixture with EtONa at $60 \degree C$ for 2 h afforded the desired 4-ethynylbenzene-sulfonamide 4a in a yield of 67 % (Table 1, entry 1).

The generality and scope of this method was thoroughly investigated under the same conditions using a diverse range of alkylamines. The results are given in Table 1. Both primary and secondary alkylamines gave good results. Primary amines such as $n$-butylamine (2b), $iso$-propylamine (2c) and 1-phenylethylamine (2d) furnished the corresponding sulfonamides 4b – d in yields of 64 – 70 % (entries 2 – 4). Secondary amines such as diethylamine (2e) and piperidine (2f) afforded the sulfonamides 4e – f in 67 and 64 % yield, respectively (entries 5 and 6). Gratifyingly, there was no limit for alkylamine substrates. In the case of aqueous ammonia (2h), the corresponding (Z)-4-(2-bromovinyl)benzenesulfonamide (4g) was also isolated in 67 % yield (entry 7).

Aniline (2h) was next examined as a model substrate for arylamines. Under the same reaction conditions as for alkylamines, almost no intermediate 3h was observed. However, addition of the same volume of pyridine instead of DMF to the reaction system and further irradiation for 40 s followed by a thermal reaction at $60 \degree C$ for 2 h in the presence of EtONa gave 4h in a satisfactory yield of 71 % (Table 1, entry 8).

Other arylamines were also tested under the same conditions as for 2h, and the results are given in Table 1 (entries 9 – 11). The reaction of $p$-tolylamine (2i) gave the corresponding sulfonamide 4i in high yield (72 %, entry 9). In the case of o-tolylamine (2j), the yield of 4j was 70 % (entry 10). This method proved to be very useful even for sterically hindered compounds such as N-methylaniline (2k); the corresponding arenesulfonamide 4k was obtained in 68 % yield (entry 11).

**Conclusion**

In summary, we have developed a facile one-pot method for selective synthesis of 4-ethynylbenzenesulfonamides.
sulfonamides from anti-2,3-dibromo-3-(4-chlorosulfonyl-phenyl)propanoic acid and various amines in good yields. 4-Ethynylbenzenesulfonamides are important synthetic targets and widely used synths in synthetic chemistry.

**Experimental Section**

Melting points were recorded using a A. Krüss Otpronic GmbH KSPII apparatus and are uncorrected. A Xinyi MAS-IF microwave synthesizer was used for all microwave reactions (800 W). IR spectra were performed on a Nexus FT-IR spectrophotometer. 1H and 13C NMR spectra were recorded with a Bruker AM-500 spectrometer on CDCl3 solutions with SiMe4 as an internal standard. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. High-resolution mass spectra were determined using a Finnigan-MAT GC/MS/DS 8430 spectrometer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF 254 silica gel coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure.

**Preparation of compound 1**

To a solution of 4-chlorosulfonylcinnamic acid (20 mmol), which was prepared according to a literature procedure [11], in HOAc (40 mL) was added bromine (40 mL). The solution was stirred at 70 °C in an oil bath for 3 h. After cooling to r.t., the solvent was removed under reduced pressure. The resulting solid was dissolved in EtOAc, washed with water and dried over anhydrous Na2SO4. The organic layer was separated. Evaporation of the solvent gave a crude product, which was recrystallized in EtOAc-hexane to yield the solvent gave a crude product, which was recrystallized from EtOAc-hexane to yield I as a white solid (93%). M. p. 197.3 – 197.5 °C. – IR (KBr): ν = 3438, 3242, 1632, 1583, 1446, 1392, 1154 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 1.09 – 1.76 (10H, m), 3.12 – 3.19 (1H, m), 3.25 (1H, s), 4.47 (1H, d, J = 7.4 Hz), 7.61 (2H, d, J = 8.6 Hz), 7.84 (2H, d, J = 8.6 Hz). – 13C NMR (125 MHz, CDCl3): δ = 26.41, 25.10, 34.00, 52.78, 80.41, 82.10, 126.51, 126.86, 132.66, 141.59. – Anal. for C14H17NO2S: calcd. C 63.90, H 6.56; found C 63.90, H 6.56.

**N-Cyclohexyl-4-ethynylbenzenesulfonamide (4a)**

Colorless liquid. – IR (KBr): ν = 3376, 1600, 1549, 1490, 1461, 1167 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 0.77 (3H, t, J = 7.4 Hz), 1.19 – 1.23 (2H, m), 1.34 – 1.39 (2H, m), 2.85 – 2.89 (2H, m), 3.18 (1H, s), 4.87 (1H, s), 7.54 (2H, d, J = 8.4 Hz), 7.76 (2H, d, J = 8.4 Hz). – 13C NMR (125 MHz, CDCl3): δ = 13.42, 19.60, 31.52, 42.90, 80.51, 81.99, 126.61, 126.96, 132.63, 140.03. – HRMS: m/z = 237.0825 (calcd. 237.0824 for C12H15NO2S, M⁺).

**4-Ethynyl-N-isopropylbenzenesulfonamide (4b)**

White solid. M. p. 124.0 – 125.0 °C. – IR (KBr): ν = 3438, 3242, 1632, 1583, 1446, 1392, 1154 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 1.09 – 1.76 (10H, m), 3.12 – 3.19 (1H, m), 3.25 (1H, s), 4.47 (1H, d, J = 7.4 Hz), 7.61 (2H, d, J = 8.6 Hz), 7.84 (2H, d, J = 8.6 Hz). – 13C NMR (125 MHz, CDCl3): δ = 26.41, 25.10, 34.00, 52.78, 80.41, 82.10, 126.51, 126.86, 132.66, 141.59. – Anal. for C14H17NO2S: calcd. C 63.90, H 6.56; found C 63.90, H 6.56.

**N-Butyl-4-ethynylbenzenesulfonamide (4c)**

White solid. M. p. 84.0 – 85.0 °C. – IR (KBr): ν = 3376, 1600, 1549, 1490, 1461, 1167 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 1.01 (6H, d, J = 7.5), 3.18 (1H, s), 3.37 – 3.41 (1H, m), 4.78 (1H, s), 7.53 (2H, d, J = 8.3 Hz), 7.78 (2H, d, J = 8.3 Hz). – 13C NMR (125 MHz, CDCl3): δ = 23.55, 46.19, 80.46, 82.02, 126.50, 126.89, 132.62, 141.19. – Anal. for C16H15NO2S: calcd. C 59.17, H 5.87; found C 59.22, H 5.93.

**4-Ethynyl-N-(1-phenylethyl)benzenesulfonamide (4d)**

White solid. M. p. 96.0 – 97.0 °C. – IR (KBr): ν = 3438, 3281, 1590, 1561, 1453, 1461, 1153 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 1.37 (3H, d, J = 7.0), 3.15 (1H, s), 4.42 – 4.45 (1H, m), 4.93 (1H, s), 6.99 – 7.01 (2H, m), 7.10 – 7.12 (3H, m), 3.73 (2H, d, J = 8.5 Hz), 7.56 (2H, d, J = 8.5 Hz). – 13C NMR (125 MHz, CDCl3): δ = 23.55, 53.85, 80.32, 82.09, 126.10, 126.38, 126.96, 127.67, 128.62, 132.38, 140.74, 141.59. – Anal. for C16H15NO2S: calcd. C 67.34, H 5.30; found C 67.39, H 5.35.

**N,N-Diethyl-4-ethynylbenzenesulfonamide (4e)**

White solid. M. p. 73.8 – 74.0 °C. – IR (KBr): ν = 3319, 3267, 1589, 1561, 1453, 1461, 1153 cm⁻¹. – 1H NMR (500 MHz, CDCl3): δ = 1.09 – 1.76 (10H, m), 3.12 – 3.19 (1H, m), 3.25 (1H, s), 4.47 (1H, d, J = 7.4 Hz), 7.61 (2H, d, J = 8.6 Hz), 7.84 (2H, d, J = 8.6 Hz). – 13C NMR (125 MHz, CDCl3): δ = 26.61, 25.10, 34.00, 52.78, 80.41, 82.10, 126.51, 126.86, 132.66, 141.59. – Anal. for C16H15NO2S: calcd. C 59.22, H 5.93.
CDCl3): δ = 1.04 (6H, t, J = 7.15 Hz), 3.16 (1H, s), 3.15 (4H, q, J = 7.15 Hz), 7.51 (2H, d, J = 8.5 Hz), 7.68 (2H, d, J = 8.5 Hz). −13C NMR (125 MHz, CDCl3): δ = 14.07, 42.00, 80.36, 82.05, 126.27, 126.88, 132.59, 140.50. − Anal. for C12H15NO2S: calcd. C 60.73, H 6.37; found C 60.64, H 6.45.

I-(4-Ethynylphenylsulfonyl)piperidine (4f)

White solid. M. p. 175.7 – 176.4 °C. − IR (KBr): ν = 3600 – 3200, 1630 – 1450, 1330 – 1100 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 4.49 (1H, t, J = 6.2 Hz), 7.34 (2H, d, J = 8.7 Hz), 7.55 (2H, d, J = 8.7 Hz). − 13C NMR (125 MHz, CDCl3): δ = 14.07, 35.84, 120.30, 132.60, 138.96. − Anal. for C15H13NO2S: calcd. C 63.35, H 4.28; found C 63.30, H 4.22.

4-Ethynylbenzenesulfonamide (4g)

White solid. M. p. 130.0 – 130.5 °C. − IR (KBr): ν = 3448, 3252, 1595, 1552, 1481, 1467, 1161 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 1.35 – 1.37 (2H, m), 1.55 – 1.59 (4H, m), 2.91 – 2.93 (4H, t, J = 5.5 Hz), 3.19 (1H, s), 7.55 (2H, d, J = 8.3 Hz), 7.64 (2H, d, J = 8.3 Hz). − 13C NMR (125 MHz, CDCl3): δ = 23.45, 25.13, 46.89, 80.57, 82.00, 126.63, 127.54, 132.52, 138.09. − Anal. for C13H15NO2S: calcd. C 62.62, H 6.06; found C 62.58, H 6.02.

General procedure for the one-pot synthesis of N-aryl-4-ethynylarylsulfonamides 4h – k

To a solution of 1 (1 mmol) in DMF (2 mL) was added an arylamine 2 (2.4 mmol). The mixture was kept inside a microwave oven and was irradiated for 25 s. To the mixture was then added pyridine (2 mL). The reaction mixture was irradiated for 40 s, removed from the oven and cooled to r. t. To the reaction mixtures was added NaOEt (4 mmol). The mixture was stirred at 60 °C in an oil bath for 2 h. After cooling to r. t., aqueous HCl (5 %) and EtOAc were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and water and dried over anhydrous Na2SO4. Evaporation of the solvent gave the crude product, which was subjected to column chromatography (silica gel, EtOAc-petroleum ether) to afford 4-ethynylbenzenesulfonamides 4h – k.

4-Ethynyl-N-phenylbenzenesulfonamide (4h)

White solid. M. p. 147.1 – 147.6 °C. − IR (KBr): ν = 3247, 1590, 1567, 1490, 1471, 1161 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 3.16 (1H, s), 6.99 – 7.01 (3H, m), 7.06 (1H, m), 7.15 – 7.19 (2H, m), 7.45 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz). − 13C NMR (125 MHz, CDCl3): δ = 80.86, 81.89, 121.99, 125.79, 127.15, 127.19, 129.42, 132.60, 138.96. − Anal. for C16H13NO2S: calcd. C 63.35, H 4.31; found C 63.30, H 4.28.

4-Ethynyl-N-p-tolylbenzenesulfonamide (4i)

White solid. M. p. 125.0 – 126.0 °C. − IR (KBr): ν = 3435, 3256, 1589, 1512, 1423, 1160 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 2.28 (3H, s), 3.23 (1H, s), 6.53 (1H, s), 6.93 (2H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.6 Hz), 7.68 (2H, d, J = 8.6 Hz). − 13C NMR (125 MHz, CDCl3): δ = 20.80, 80.74, 81.94, 122.65, 126.97, 127.21, 129.94, 132.54, 133.26, 135.85, 139.00. − Anal. for C16H13NO2S: calcd. C 64.40, H 4.83; found C 64.45, H 4.88.

4-Ethynyl-N-o-tolylbenzenesulfonamide (4j)

White solid. M. p. 126.0 – 127.0 °C. − IR (KBr): ν = 3438, 3309, 1622, 1586, 1489, 1383, 1163 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 2.00 (3H, s), 3.25 (1H, s), 6.47 (1H, s), 7.09 – 7.30 (4H, m), 7.53 (2H, d, J = 8.6 Hz), 7.68 (2H, d, J = 8.6 Hz). − 13C NMR (125 MHz, CDCl3): δ = 17.54, 80.83, 81.92, 124.75, 126.66, 127.05, 127.08, 130.91, 131.75, 132.57, 134.00, 139.62. − Anal. for C16H13NO2S: calcd. C 66.40, H 4.83; found C 66.46, H 4.80.

4-Ethynyl-N-methyl-N-phenylbenzenesulfonamide (4k)

White solid. M. p. 126.0 – 127.0 °C. − IR (KBr): ν = 3271, 1600, 1509, 1485, 1171 cm−1. − 1H NMR (500 MHz, CDCl3): δ = 3.11 (3H, s), 3.19 (1H, s), 7.00 – 7.02 (2H, m), 7.19 – 7.25 (3H, m), 7.42 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 9.0 Hz). − 13C NMR (125 MHz, CDCl3): δ = 38.18, 80.72, 81.99, 126.62, 126.82, 127.51, 127.74, 128.96, 132.30, 136.75, 141.23. − Anal. for C17H13NO2S: calcd. C 66.40, H 4.83; found C 66.38, H 4.79.

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