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 plaguicides [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].

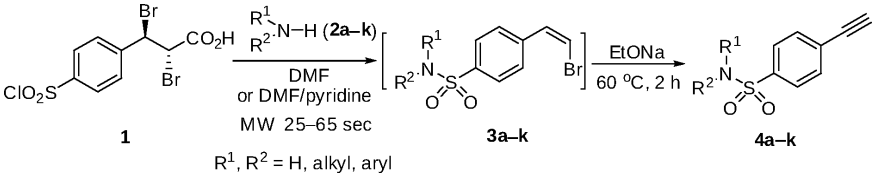
Arylacetylenes are also useful and versatile intermediates in organic synthesis. Their use as precursors for the synthesis of oligo(arylenealkyne) macrocycles [6] has stimulated a great deal of interest in their synthesis. More recently, benzenesulfonamides containing a 4-ethynyl substituent were frequently 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 alkyne reagents were needed in the presently used synthetic method [8], which involves the coupling reaction between 4-bromobenzene sulfonamide and ethynyltrimethylsilane 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*)-arylvinyl 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*)-arylvinyl bromides was made on the basis of ^{1}H NMR spectra. The ^{1}H NMR spectrum of Ar-CH=CH–Br exhibits an AA′BB′-type pattern. Particularly, (*Z*) and (*E*) vicinal



Scheme 1.

Table 1. Synthesis of 4-ethynylarylsulfonamides **4**.

Entry	Amine **2**				Condition[a]	Product **4**[b,c]	Yield (%)
			R^1	R^2			
1		**2a**		H-	A	**4a**	67
2	*n*-$BuNH_2$	**2b**	*n*-Bu-	H-	A	**4b**	70
3	*i*-$PrNH_2$	**2c**	*i*-Pr-	H-	A	**4c**	75
4	$PhCH(Me)NH_2$	**2d**	PhCH(Me)-	H-	A	**4d**	64
5	$(Et)_2NH$	**2e**	Et-	Et-	A	**4e**	67
6		**2f**	$-(CH_2)_5-$		A	**4f**	64
7	$NH_3 \cdot H_2O$	**2g**	H-	H-	A	**4g**	67
8	$PhNH_2$	**2h**	Ph-	H-	B	**4h**	71
9	*p*-$MeC_6H_4NH_2$	**2i**	*p*-tolyl	H-	B	**4i**	72
10	*o*-$MeC_6H_4NH_2$	**2j**	*o*-tolyl	H-	B	**4j**	70
11	$PhNHCH_3$	**2k**	Ph-	Me-	B	**4k**	68

[a] Condition A: 1) substrate **1** (1 mmol), alkylamine **2** (2.4 mmol), DMF (3 mL), MW 25 s, 2) EtONa (4 mmol), 60 °C, 2 h; Condition B: 1) substrate **1** (1 mmol), arylamine **2** (2.4 mmol), DMF (2 mL), MW 25 s, 2) pyridine (2 mL), MW 40 s, 3) EtONa (4 mmol), 60 °C, 2 h; [b] isolated yields; [c] intermediate **3**: $Z/E > 99/1$, determined by ^{1}H NMR analysis.

coulping 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 °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*)-arylvinyl 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 °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 (**2g**), 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 °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-ethynylbenzene-

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 synthons in synthetic chemistry.

Experimental Section

Melting points were recorded using a A. Krüss Optronic GmbH KSPII apparatus and are uncorrected. A Xinyi MAS-II microwave synthesizer was used for all microwave reactions (800 W). IR spectra were performed on a Nexus FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM-500 spectrometer on $CDCl_3$ solutions with $SiMe_4$ 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 Na_2SO_4. The organic layer was separated. Evaporation of the solvent gave a crude product, which was recrystallized from EtOAc-hexane to yield **1** as a white solid (93 %). M. p. 197.3 – 197.5 °C. – IR (KBr): ν = 1681, 1334, 1164 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.84 (1H, d, J = 12.0 Hz), 5.37 (1H, d, J = 12.0 Hz), 7.69 (2H, d, J = 8.4 Hz), 8.09 (2H, d, J = 8.4 Hz). – Anal. for $C_9H_7Br_2ClO_4S$: calcd. C 26.59, H 1.74; found C 26.52, H 1.70.

*General procedure for the one-pot synthesis of N-alkyl-4-ethynylbenzenesulfonamides **4a – g***

An alkylamine **2** (2.4 mmol) was added to a solution of **1** (1 mmol) in DMF (3 mL). The mixture was kept inside a microwave oven and was irradiated for 25 s. The reaction mixture was then 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 washed with brine and water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was subjected to column chromatography (silica gel, EtOAc-petroleum ether) to afford 4-ethynylbenzenesulfonamides **4a – g**.

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

White solid. M. p. 124.0 – 125.0 °C. – IR (KBr): ν = 3438, 3242, 1632, 1583, 1446, 1392, 1154 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.61, 25.10, 34.00, 52.78, 80.41, 82.10, 126.51, 126.86, 132.66, 141.59. – Anal. for $C_{14}H_{17}NO_2S$: calcd. C 63.85, H 6.51; found C 63.90, H 6.56.

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

Colorless liquid. – IR (KBr): ν = 3376, 1600, 1561, 1490, 1461, 1167 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{12}H_{15}NO_2S$, M^+).

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

White solid. M. p. 84.0 – 85.0 °C. – IR (KBr): ν = 3319, 3267, 1589, 1561, 1485, 1467, 1161 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.65, 46.19, 80.46, 82.02, 126.50, 126.89, 132.62, 141.19. – Anal. for $C_{11}H_{13}NO_2S$: 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, 1543, 1461, 1153 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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), 7.37 (2H, d, J = 8.5 Hz), 7.56 (2H, d, J = 8.5 Hz). – ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{16}H_{15}NO_2S$: 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, 1604, 1575, 1514, 1461, 1157 cm^{-1}. – ^{1}H NMR (500 MHz,

$CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.07, 42.00, 80.36, 82.05, 126.27, 126.88, 132.59, 140.50. – Anal. for $C_{12}H_{15}NO_2S$: calcd. C 60.73, H 6.37; found C 60.64, H 6.45.

*1-(4-Ethynylphenylsulfonyl)piperidine (**4f**)*

White solid. M. p. 134.0 – 135.0 °C. – IR (KBr): ν = 3448, 3252, 1595, 1552, 1481, 1467, 1161 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.45, 25.13, 46.89, 80.57, 82.00, 126.63, 127.54, 132.52, 138.09. – Anal. for $C_{13}H_{15}NO_2S$: calcd. C 62.62, H 6.06; found C 62.58, H 6.02.

*4-Ethynylbenzenesulfonamide (**4g**)*

White solid. M. p. 175.7 – 176.4 °C. – IR (KBr): ν = 3356, 3262, 3090, 1592, 1546, 1486, 1396, 1157 cm^{-1}. – ^{1}HNMR (500 MHz, $CDCl_3$): δ = 3.26 (1H, s), 4.83 (2H, s), 7.63 (2H, d, J = 8.6 Hz), 7.89 (2H, d, J = 8.6 Hz). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.17, 126.03, 129.14, 131.31, 138.25, 143.55.

*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 Na_2SO_4. 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}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 80.86, 81.89, 121.99, 125.79, 127.15, 127.19, 129.42, 132.60, 138.96. – Anal. for $C_{14}H_{11}NO_2S$: 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}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{15}H_{13}NO_2S$: calcd. C 66.40, H 4.83; found C 66.45, H 4.88.

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

White solid. M. p. 136.0 – 137.0 °C. – IR (KBr): ν = 3438, 3309, 1622, 1586, 1489, 1383, 1163 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{15}H_{13}NO_2S$: 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, 1552, 1509, 1485, 1171 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): 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). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.18, 80.72, 81.99, 126.62, 126.82, 127.51, 127.74, 128.96, 132.30, 136.57, 141.23. – Anal. for $C_{15}H_{13}NO_2S$: calcd. C 66.40, H 4.83; found C 66.38, H 4.79.

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