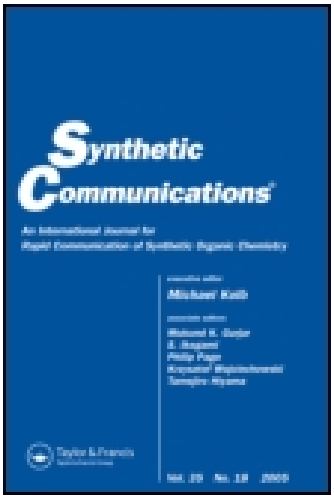

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Synthesis of Tetrahydrobenzazepinesulfonamides and Their Rearrangement to Diarylsulfones

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Synthesis of Tetrahydrobenzazepinesulfonamides and Their Rearrangement to Diarylsulfones

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Abstract: A new class of diarylsulfones, in which tetrahydrobenzazepine comprises one of the aromatic moieties, has been synthesized via the acid-catalyzed rearrangement of several substituted benzazepinesulfonamides. The rearrangement is normally *ortho* but in at least one case a *para* isomer is also formed. Sulfones of this type have been shown to possess potent anti-HIV activity.

Keywords: Acid-catalyzed rearrangements, benzazepine, sulfonamides, sulfones

INTRODUCTION

In earlier work from this laboratory, the rearrangement of tetrahydroquinolinesulfonamides **(A)** to diarylsulfones **(B)** was described.[1] The reaction is an extension of the acid-catalyzed rearrangement of N-alkylbenzenesulfonanilides,[1] originally described by Witt and Uermenyi[2] and expanded on by Halberkamm.[3] In this reaction the benzenesulfonyl group migrates primarily to the *ortho* position although in special cases some *para* isomer is formed. The mechanism of rearrangement[1] for these sulfonamides **(C)** has also been investigated. Recently diarylsulfones[4] and in particular

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several of the sulfones prepared in this laboratory have been shown to be potent non-nucleoside reverse transcriptase inhibitors (NNRTI's) of HIV.[5] See Figure 1.

With this renewed interest in diarylsulfones, research in this lab was initiated with the goal of preparing new diarylsulfones possessing a fused-ring containing a nitrogen atom. Specifically the preparation and rearrangement of sulfonamides derived from indoline **(D)** and tetrahydrobenzazepine **(E)** were undertaken. Unfortunately the indolinesulfonamides did not undergo acid-catalyzed rearrangement but simply hydrolyzed. This article describes the synthesis and rearrangement of tetrahydrobenzazepine-sulfonamides.

RESULTS AND DISCUSSION

The preparation of 2,3,4,5-tetrahydrobenzazepine from α-tetralone **(1)** has been described.[6] The tetralone is converted to an oxime **(2)**, which, when treated with polyphosphoric acid (PPA), undergoes a Beckmann rearrangement to tetrahydrobenzazepinone **(3)**.[7] Lithium aluminum hydride reduction of the lactam yielded the tetrahydrobenzazepine **(4)**.[8]

For this work the 7-chloro-2,3,4,5-tetrahydrobenzazepine **(6)** was also desired to add diversity to the series and, because the 7-chloro isomer in the tetrahydroquinoline series,[5] showed excellent activity. A novel synthesis of **(6)** was achieved by chlorinating the lactam **(3)** using sulfuryl chloride and then reducing the product **(5)** to compound **(6)**. A small percentage of the chlorolactam consisted of the 9-isomer but it could be removed by recrystallization. Scheme 1 outlines the synthetic routes.

The benzazepinesulfonamides were prepared by reacting compounds **(4)** or **(6)** with benzenesulfonyl chloride or 2-nitrobenzenesulfonyl chloride to give four sulfonamides, two of which **(9, 10)** were novel and two known **(7, 8)** compounds.[9,10] When treated with 98% sulfuric acid, the four amides rearranged to form five new sulfones **(11–15)**. Compound **(8)** with a 2-nitro-group and no 7-substituent gave mainly the *ortho* rearranged product **(12)** but also formed a small amount of the *para* sulfone **(15)** (Scheme 2). The *para* isomer comprised about 10% of the rearranged product.

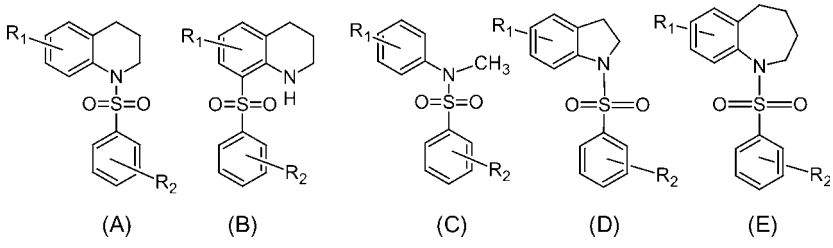
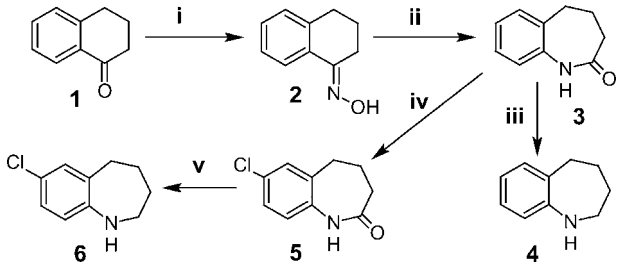


Figure 1. Sulfones and sulfonamides under investigation.



Scheme 1. (i) NH_2OH, pyridine, MeOH, reflux; (ii) PPA, 120°, and then iced; (iii) $LiAlH_4$, THF, refluxed 4 h; (iv) SO_2Cl_2, benzene, 0–5°, then rt, 3 h; (v) $LiAlH_4$, THF, refluxed 4 h.

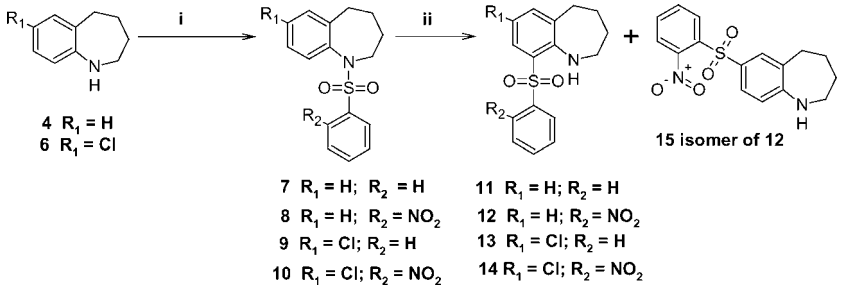
Table 1 lists the sulfonamides and sulfones which were prepared and characterized.

EXPERIMENTAL

All melting points are uncorrected. All infrared spectra (FT-IR) were recorded with thin film on a KBr plate and only noteworthy absorptions (cm^{-1}) are listed. ^1H NMR spectra were recorded at 400 MHz with TMS as an internal reference. All mass spectra were determined with a GC-MS. The results of elemental analysis are within $\pm 0.3\%$ of the theoretical values.

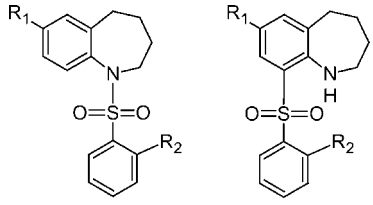
Synthesis of α-Tetralone Oxime (2)[6]

A mixture of 25.6 g (17.5 mmol) of α-tetralone **(1)**, 25.7 g (37.2 mmol) of hydroxylamine hydrochloride, 125 mL of pyridine, and 125 mL of methanol were added to a 500-mL, three-necked, round-bottomed flask. The solution was refluxed for 2 h, resulting in a clear green solution. Green crystals of



Scheme 2. (i) R_2BzSO_2Cl, 10% NaOH, warm to 50°; (ii) 98% H_2SO_4 at 105° for 20 min; pour over ice.

Table 1. Preparation of sulfonamides and sulfones



Type I Type II

No.	Type	R_1	R_2	Mp (°C)	Formula	Yield (%)
7[a]	I	H	H	111–112	$C_{16}H_{17}NO_2S$	78
8[b]	I	H	NO_2	127.5–129	$C_{16}H_{16}N_2O_4S$	58
9	I	Cl	H	148–149	$C_{16}H_{16}ClNO_2S$	95
10	I	Cl	NO_2	142.5–144	$C_{16}H_{15}ClN_2O_4S$	79
11	II	H	H	84–85.5	$C_{16}H_{17}NO_2S$	45
12	II	H	NO_2	89–91	$C_{16}H_{16}N_2O_4S$	20
13	II	Cl	H	147–148.5	$C_{16}H_{16}ClNO_2S$	52
14	II	Cl	NO_2	99–101.5	$C_{16}H_{15}ClN_2O_4S$	49
15	II	H@9	NO_2	181–183	$C_{16}H_{16}N_2O_4S$	2

[a]Compound **7** is known (mp 10°, Ref. [6]).

[b]Compound **8** is known (no data, Ref. [7]). H@9 = 2-NO_2PhSO_2-group at position 7 (from *para*-rearrangement); isomer of compd. **12**.

α-tetralone oxime were obtained after the solvent was evaporated. The sample was further recrystallized from 95% ethanol to give 26 g of light green crystals. Yield: 92.3%; mp: 106–108 ° (lit. mp: 100.5–101.5 °).[6] IR: 3248.17 cm^{-1}(O–H), 1638.53 cm^{-1} (C═N), 951.17 cm^{-1} (N–O); ^{1}H NMR ($CDC1_3$): δ 7.92–7.04 (m, 4H, aromatics), 2.89–2.86 (t, 2H, CH_2), 2.81–2.78 (t, 2H, CH_2), 1.95–1.89 (m, 2H, CH_2). GC-MS: m/z 162 (M^+).

Synthesis of l,3,4,5-Tetrahydro-2*H*-1-benzazepin-2-one (3)[7]

A mixture of 3.07 g (19.1 mmol) of **(2)** and 44.92 g of polyphosphoric acid (PPA) were placed in a 500-mL beaker. Then the mixture was heated to 120° in an oil bath under constant stirring. The color of the mixture gradually darkened. The viscosity of the mixture, caused mainly by PPA, decreased as the temperature reached 120°. The reaction was then kept at 120–130° for another 10 min. The temperature was allowed to return to room temperature, and then ice was added to the cherry-red reaction mixture. Six or seven h later, a pale precipitate formed and was filtered and washed with water, resulting in 2.43 g of **(3)**. Yield: 78.14%; mp:143–145° (lit. mp: 142.5–143°).[7] IR: 3187.67 cm^{-1} (NH), 1661.18 cm^{-1} (C–O); ^{1}H NMR ($CDCl_3$): δ 7.64 (bs, 1H, NH), 7.28–6.98 (m, 4H, aromatics),

2.85–2.88 (t, 2H, CH_2), 2.40–2.37 (t, 2H, CH_2), 2.29–2.22 (m, 2H, CH_2). GC-MS: m/z 161 (M^+).

Synthesis of 2,3,4,5-Tetrahydro-l*H*-l-benzazepine (4)[8]

Pulverized lithium aluminum hydride (1.5 g, 39.5 mmol) and 15 mL of dry THF were placed into a 500-mL, three-necked, round-bottomed flask, and the mixture heated to boiling. A solution of 3.7 g (22.9 mmol) of **(3)** in 150 mL of dry THF was added slowly at such a rate that the solvent refluxed gently without external heating. When the addition was complete, the solution was stirred and heated at reflux for 4 h. After the reaction mixture cooled, water was added dropwise to destroy the excess $LiAlH_4$. A gray precipitate was removed by gravity filtration and washed with $CHC1_3$ several times. The gray precipitate was extracted with $CHC1_3$ using a Soxhlet extraction apparatus for 6 h. The chloroform washings and chloroform extract were combined and the solvent stripped to give 2.40 g (yield: 74.1%) of a reddish viscous liquid. Compound **(4)** was reported to have a melting point of 32°.[8] The crude product was used directly to prepare tetrahydrobenzazepinesulfonamides. IR: 3360.86 cm^{-1} (NH), stretch absorption of C═O at 1661.18 cm^{-1} disappeared; ^1H NMR ($CDC1_3$): δ 7.16–6.66 (m, 4H, aromatics), 3.81 (bs, 1H, NH), 3.10–3.07 (t, 2H, CH_2), 2.83–2.80 (t, 2H, CH_2), 1.85–1.81 (m, 2H, CH_2), 1.71–1.67 (m, 2H, CH_2).

Synthesis of 7-Chloro-2,3,4,5-tetrahydro-2*H*-l-benzazepin-2-one (5)[11]

Dry benzene (20 mL) and 3 g (18.6 mmol) of **(3)** were placed in a round-bottomed flask. To this solution, 3 mL of SO_2Cl_2 in 10 mL of dry benzene was added dropwise, under constant stirring, while the temperature was kept at 0-5° using an ice–water bath. The solution was stirred for an additional 40 min after the addition was complete. The solution was then stirred at room temperature for 3 h longer. The solvent and excess SO_2Cl_2 were removed using a water aspirator, leaving a yellow solid. The crude product **(5)** was recrystallized from ethyl acetate or acetone to give 1.37 g of white crystals. Yield 37.7%; mp: 161–163° (lit. mp: 164–166°).[11] IR: 3306.27 cm^{-1} (NH), 1667.67 cm^{-1} (C═O); ^1H NMR (DMSO-d_6): δ 9.56 (s, 1H, NH), 6.96–7.36 (3H, aromatics), 2.67–2.70 (t, 2H, CH_2), 2.06–2.18 (m, 4H, CH_2CH_2). GC-MS: m/z 195 (M^+).

Synthesis of 7-Chloro-2,3,4,5-tetrahydro-l*H*-l-benzazepine (6)

Using the same procedure for **(4)**,[8] 0.93 g (24.5 mmol) of pulverized lithium aluminum hydride, 15 mL of dry THF, and 2.45 g (12.6 mmol) of **(5)** were

reacted. A gray-white precipitate was collected by gravity filtration and was washed with THF. After the THF was evaporated, 2.40 g of a pale solid was obtained. Yield: 88.1%; mp 66–67°. IR: 3374.99 cm^{-1} (NH), stretch absorption of C═O at 1667.67 cm^{-1} disappeared; ^1H NMR ($CDC1_3$): δ 6.69–7.10 (4H, aromatics), 4.07 (bs, NH), 3.03–3.05 (t, 2H, CH_2), 2.74–2.76 (t, 2H, CH_2), 1.79–1.83 (m, 2H, CH_2), 1.64–1.68 (m, 2H, CH_2). GC-MS m/z 181 (M^+).

Synthesis of 1-Benzenesulfonyl-2,3,4,5-tetrahydro-l*H*-l-benzazepine (7)[9]

Compound **(4)** (3.10 g, 20 mmol) and 3.71 g (20 mmol) of benzenesulfonyl chloride were placed in a 100-mL beaker. Aqueous sodium hydroxide solution (10%) was added slowly under constant stirring. The reaction mixture became warm and a gummy solid started to form. Enough aqueous sodium hydroxide solution was added to keep the solution basic. The solution was then warmed to 50° for several minutes. The supernatant liquid was decanted, and the resulting gummy mass washed with water and recrystallized (using charcoal) from ethanol to yield 4.60 g of light yellow needles. Yield: 78.3%; mp: 111–112°. (lit. 109°).[9] IR: 1140.12 cm^{-1} and 1379.10 cm^{-1} (S═O); ^1H NMR ($CDCl_3$): δ 7.11–7.76 (m, 9H, aromatics), 3.72–3.77 (bs, 2H, CH_2), 2.36–2.39 (t, 2H, CH_2), 1.80–1.85 (m, 2H, CH_2), 1.56 (bs, 2H, CH_2). GC-MS: m/z 287 (M^+).

Synthesis of 1-[2-Nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine (8)

Using the same procedure as **(7)**, 2.02 g (13.7 mmol) of **(4)** and 3.18 g (14.4 mmol) of 2-nitrobenzenesulfonyl chloride were reacted to yield 2.63 g of light yellow needles. Yield: 57.8%; mp: 127.5–129°. IR: No NH absorption at 3500–3100 cm^{-1}, 1153.46 cm^{-1}, and 1339.40 cm^{-1} (SO); ^1H NMR ($CDC1_3$): δ 7.84–7.70 (m, 4H, aromatics), 7.26–6.87 (m, 4H, aromatics), 3.77 (bs, 2H, CH_2), 2.87–2.85 (t, 2H, CH_2), 2.02–1.96 (m, 2H, CH_2), 1.70 (bs, 2H, CH_2). GC-MS: m/z 332 (M^+).

Synthesis of 7-Chloro-l-(phenylsulfonyl)-2,3,4,5-tetrahydro-l*H*-l-benzazepine (9)

Pyridine (5.3 mL) was added to a mixture of 0.96 g (5.5 mmol) of **(6)** and 1.75 g (9.9 mmol) of benzenesulfonyl chloride in a 25-mL, round-bottomed flask. The solution turned red and was refluxed for 3 h, then cooled. The reaction mixture was poured over ice, and a yellow product precipitated.

The solid was filtered and recrystallized from ethanol to give 1.2 g of white needles. Yield: 94.7%; mp 148–149°; IR: 1158.42 cm^{-1} and 1343.41 cm^{-1} (S═O); ^1H NMR ($CDCl_3$): δ 1.55 (bs, 2H, CH_2), 1.78–1.83 (m, 2H, CH_2), 2.29–2.32 (t, 2H, CH_2), 3.71 (bs, 2H, CH_2), 7.12–7.75 (8H, aromatics). GC-MS: m/z 321 (M^+); Anal. calcd. for $C_{16}H_{16}ClNO_2S$: C, 59.72%; H, 5.01%; N, 4.35%. Found: C, 59.53%; H, 4.87%; N, 4.43%.

Synthesis of 7-Chloro-1-[2-Nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine (10)

Using the same procedure as **(9)**, a mixture of 0.92 g (5.08 mmol) of **(6)** and 2.02 g (9.11 mmol) of 2-nitrobenzenesulfonyl chloride were reacted and recrystallized from hexane/acetone to give 1.47 g of orange or yellow crystals. Yield: 78.9%; mp 142.5–144°; IR: 1158.82 cm^{-1} and 1355.22 cm^{-1} (S═O); ^1H NMR ($CDC1_3$): δ 1.69 (bs, 2H, CH_2), 1.94–2.00 (m, 2H, CH_2), 2.80–2.81 (t, 2H, CH_2), 3.71 (bs, 2H, CH_2), 6.82–7.25 (m, 3H, aromatics), 7.63–7.85 (m, 4H, aromatics). GC-MS: MS: m/z 366 (M^+).

Synthesis of 9-(Phenylsulfonyl)-2,3,4,5-tetrahydro-l*H*-l-benzazepine (11): Rearrangement of (7)

A mixture of 2.0 g (6.96 mmol) of l-(phenylsulfonyl)-2,3,4,5-tetrahydro-l*H*-1-benzazepine **(7)** and 8 mL of conc. H_2SO_4 was placed in a 25-mL Erlenmeyer flask. The flask was stoppered loosely with a cork, and the mixture gradually colored to a deep red. When the solid dissolved completely, the solution was heated in an oven at 105° for 20 min, cooled, and then poured onto ice with stirring until a gummy solid formed. The gummy solid was filtered and washed thoroughly with ice water until the washings were neutral. The product of **(7)** was recrystallized from methanol to give 0.89 g of yellow crystals, mp: 84–85.5°. Yield: 44.5%. IR: 3396.39 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ1.60–1.62 (m, 2H, CH_2), 1.69–1.72 (m, 2H, CH_2), 2.79–2.85 (m, 4H, CH_2), 6.11 (bs, 1H, NH), 6.89–7.90 (m, 8H, aromatics). GC-MS: m/z: 287 (M^+). Anal. calcd. for: $C_{16}H_{17}NO_2S$: C, 66.87%; H, 5.41%. Found: C, 66.87%; H, 4.87%.

Synthesis of 9-[2-Nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-1-benzazepine (12) and 7-[2-Nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-1-benzazepine (15): Rearrangement of (8)

A mixture of 2.0 g (6.0 mmol) of l-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-1-benzazepine **(8)** and 6 mL of conc. H_2SO_4 was placed in a 25-mL Erlenmeyer flask and loosely stoppered with a cork. The mixture gradually

colored. When the solid dissolved completely, the solution was heated in an oven at 105° for 15 min, cooled, and poured onto ice with stirring until a gummy solid formed. The gummy solid was filtered and washed thoroughly with ice water until the washings were neutral. The gummy solid was extracted for 15 h with ether using a Soxhlet extraction apparatus. The ether extract, after removal of solvent, yielded a yellow solid.

The crude sample contained two isomeric diarylsulfones: 9-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(12)** (major) and 7-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(15)** (minor). To effect separation, the crude sample was chromatographed on a silica-gel plate using an eluant of hexane and ethyl acetate (hexane–EtOAc = 60 : 10 and gradually increased to (hexane–EtOAc = 50 : 50). The product, 9-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(12)**, was first eluted (TLC R_f 0.44 (hexane–EtOAc = 50 : 50) as an orange or light yellow crystal (0.20 g) with a melting point at 89–91°. Yield: 20%. Next to elute as a yellow crystal (0.02 g) with a melting point of 181–183° was 7-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(15)**. The TLC R_f was 0.26 (hexane–EtOAc = 50 : 50). Yield: 2%. The molar ratio of **(12)** to **(15)** was about 10 : 1.

For 9-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(12)**, IR: 3410.66 cm^{-1} (NH); ^1H NMR ($CDC1_3$): δ 8.20–8.16 (m, 1H), 7.81–7.74 (m, 3H), 7.67–7.65 (dd, 1H), 7.33–7.32 (dd, 1H), 6.90–6.86 (t, 1H), 6.12 (bs, 1H), 3.03–3.01 (t, 2H), 2.88–2.85 (t, 2H), 1.80–1.75 (m, 2H), 1.73–1.66 (m, 2H); GC-MS: m/z 332 (M^+). Anal. calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82%; H, 4.85%; N, 8.43%. Found: C, 57.63%; H, 5.02%; N, 8.48%.

For 7-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(15)**, IR: 3387.60 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 8.30–8.28 (dd, 1H), 7.75–7.65 (m, 5H), 6.88–6.86 (d, 2H), 3.25–3.23 (t, 2H), 2.91–2.88 (t, 2H), 1.92–1.84 (m, 2H), 1.80–1.75 (m, 2H); GC-MS: m/z 332 (M^+).

Synthesis of 7-Chloro-9-(phenylsulfonyl)-2,3,4,5-tetrahydro-l*H*-l-benzazepine (13): Rearrangement of (9)

The experimental procedure is similar to the rearrangement of **(7)**; 3.11 g **(9)** and 10 mL of conc. sulfuric acid were heated in an oven for 20 min, forming a dark, clear solution. The solution was cooled and poured onto ice, resulting in a light orange precipitate. The sample was extracted for 12 h with ether using a Soxhlet apparatus to obtain the crude product, which was recrystallized from ether (by allowing the ether to evaporate until incipient crystallization) to produce 1.66 g of pure product. Yield: 51.8%; mp: 147–148.5°; IR: 3397.71 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.60–1.64 (m, 2H, CH_2), 1.68–1.72 (m, 2H, CH_2), 2.76–2.78 (t, 2H, CH_2), 2.82–2.85 (t, 2H, CH_2), 6.08 (bs, 1H, NH), 7.26–7.90 (m, 7H, aromatics). GC-MS: m/z 321 (M^+). Anal. calcd. for $C_{16}H_{16}ClNO_2S$: C, 59.72%; H, 5.01%; N, 4.35%. Found: C, 59.92%; H, 5.02%; N, 4.41%.

Synthesis of 7-Chloro-9-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine (14): Rearrangement of (10)

The experimental procedure was similar to the rearrangement of **(7)**. A mixture of 2.19 g **(10)** and 5 mL of conc. H_2SO_4 were heated for 20 min. Unlike the rearrangement of **(8)** where two isomeric sulfones were obtained, the rearrangement of 7-chloro-l-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-l*H*-l-benzazepine **(10)** only led to 7-chloro-9-[2-nitrophenylsulfonyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine. This was developed on prep-scale silica-gel TLC plates ($CHCl_3$–EtOAc; 9 : 1) to give 1.08 g of yellow crystals. Yield: 49.3%; mp 99–101.5°; IR: 3408.95 cm^{-1} (NH); ^1H NMR ($CDC1_3$): δ 1.70–1.81 (m, 4H, CH_2CH_2), 2.82–2.85 (t, 2H, CH_2), 3.05–3.08 (t, 2H, CH_2), 7.27–8.21 (m, 6H, aromatics). GC-MS: m/z 366 (M^+). Anal. calcd. for $C_{16}H_{15}ClN_2O_4S$: C, 52.39%; H, 4.12%. Found: C, 52.47%; H, 4.14%.

CONCLUSION

The syntheses described can be used to prepare a new class of diarylsulfone in which one of the aromatic moieties possesses a fused azepine ring. These compounds, like their tetrahydroquinoline analogs, may possess anti-HIV activity.

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