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Efficient syntheses of 1,2,3,4,4a,5-hexahydro-pyrazino[2,1-*c*][1,4]-benzothiazine-6,6-dioxide

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ABSTRACT

Expeditious routes to 1,2,3,4,4a,5-hexahydro-pyrazino[2,1-*c*][1,4]benzothiazine-6,6-dioxide, a methylenesulfone-constrained arylpiperazine, have been developed. The key step forms the tricyclic system in a cascade of reactions via a 1,4-addition, nitrogen alkylation, and aromatic substitution sequence.

1. Introduction

1-Arylpiperazines constitute one of the largest classes of G-protein-coupled receptors (GPCRs).[1] Constrained analogs in which the piperazine and aromatic rings are connected by a two-atom linker have been targeted as potentially more selective or higher affinity ligands for GPCRs (Fig. 1). These two-atom linkers have included ethylene (**1**),[2a] amide (**2**),[2b] aminomethylene (**3**),[2c] and sulfonylmethylene groups (**4**).[2d] The last constrained system was especially intriguing as it was incorporated into larger molecules as potential serotonergic ligands. The reported preparation of **4** involved a lengthy, stepwise introduction of the second and third rings. A continuing interest in constrained arylpiperazines led us to investigate other approaches to the 1,2,3,4,4a,5-hexahydro-pyrazino[2,1-*c*][1,4]benzothiazine-6,6-dioxide system. We report here efficient syntheses, which incorporate reaction cascades to form tricyclic **4**.

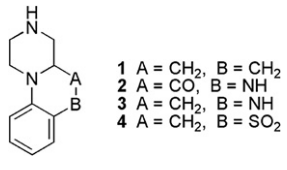

Figure 1. Examples of constrained 1-arylpiperazines.

Our approach to **4** was based on a key cascade of several steps, reacting a two nucleophile component with an electrophile incorporating three reactive positions (Fig. 2). Retrosynthetically, **4** would arise from a 1-(arylsulfonyl)-3-chloro-1-propene, which incorporated three electrophilic centers: an α,β-unsaturated sulfone, an allylic chloride, and an *ortho*-halogenated arylsulfone. Reaction of ethylenediamine with such an arylsulfone should result in sequential addition of one nitrogen to the α,β-unsaturated sulfone (*step a*), then displacement of the chloride by the second amine to form a piperazine (*step b*), and finally intramolecular substitution of the halogen *ortho* to the sulfone on the aromatic ring by the first nitrogen (*step c*) completing the tricyclic system. The addition of amines to α,β-unsaturated sulfones is a facile reaction and would likely occur first.[3] It was anticipated that the intramolecular nature of the second and third steps would accelerate these reactions thus limiting potential intermolecular side reactions. 1-(Arylsulfonyl)-3-chloro-1-propenes can be synthesized directly from 3-(arylsulfonyl)-1-propenes by palladium-catalyzed

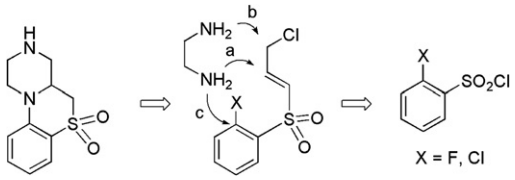

Figure 2. Retrosynthetic analysis.

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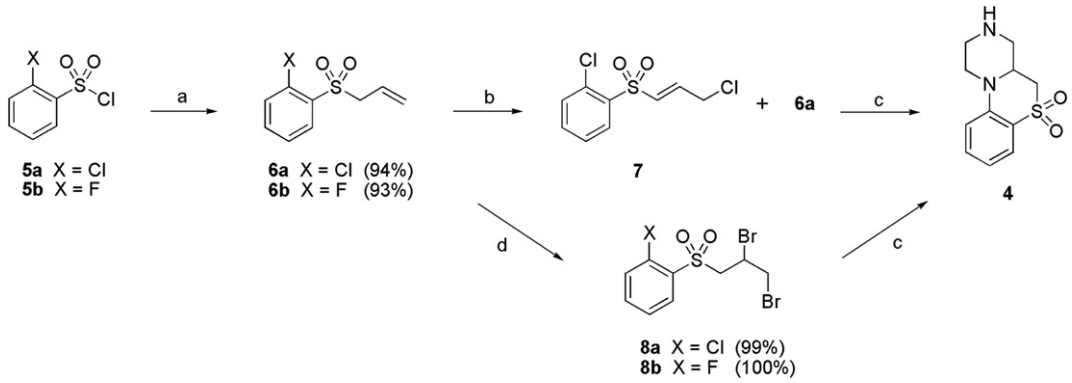
oxidative halogenation[6] and the latter propenes can, in turn, be accessed from commercially available arylsulfonyl chlorides.

2. Results and discussion

A short synthesis of key intermediate **7** was targeted for the preparation of **4** (Scheme 1). Requisite 3-(arylsulfonyl)-1-propene **6a** was made in one pot by sodium sulfite-mediated reduction of arylsulfonyl chloride **5a** to the corresponding sulfinic acid followed by two-phase alkylation with allyl bromide in the presence of a phase-transfer catalyst.[4] We have used a similar one pot approach to synthesize chloromethylarylsulfones using bromochloromethane in place of allyl bromide.[5] Using this process, fluoro analog **6b** was also prepared reasoning that fluorine might be more readily displaced in a subsequent intramolecular aromatic substitution. Conversion of sulfone **6a** into arylsulfone **7** was accomplished in one-step following the procedure of Ogura[6] by heating with $CuCl_2$, catalytic $PdCl_2$, and NaCl in acetic acid. Unfortunately, even on prolonged heating, **7** was accompanied by significant amounts of **6a** and separation of the two compounds was difficult. However, a portion of purified **7** was obtained from the mixture and used in the key cyclization reaction proposed in Figure 2. Heating **7** with three equivalents of ethylenediamine in 2-ethoxyethanol for 48 h gave the desired tricyclic **4** in good yield (71%) after converting the purified free amine to the hydrochloride salt.



Scheme 1. Reagents and conditions: (a) Na_2SO_3 (1.87 equiv), $NaHCO_3$ (2.0 equiv), H_2O, 100 °C, 1.5 h, then (*n*-Bu)$_4$NBr (cat), allyl bromide, 75 °C, 16 h; (b) $CuCl_2$ (6 equiv), $PdCl_2$ (0.03 equiv), NaCl (13 equiv), AcOH, 80 °C, 2 d; (c) $H_2NCH_2CH_2NH_2$ (3–4 equiv), $EtOCH_2CH_2OH$ (0.1 M), 130–135 °C, 24–48 h; (d) Br_2 (1.1 equiv), CH_2Cl_2, 3–4 h, rt.

The success of this strategy for an efficient preparation of tricyclic **4** led us to seek an alternative sequence avoiding the palladium-catalyzed oxidative rearrangement. One approach would be to convert alkene **6a** to the corresponding dibromide **8a** and subject the dibromide to ethylenediamine as above to effect a cascade of two amine displacements of the two bromides followed by intramolecular aromatic substitution reaction to form the tricyclic system. Bromination of **6a** afforded **8a** in essentially quantitative yield as anticipated from literature precedent.[7] Refluxing **8a** with four equivalents of ethylenediamine for 48 h afforded **4** directly in a comparable yield to that obtained with **7**. Since treatment of dibromides like **8a** with amines is known to cause elimination to the bromo analog of α,β-unsaturated sulfone **7**, cyclization likely proceeds by an initial elimination to the α,β-unsaturated sulfone followed by a similar cascade to that postulated earlier (Fig. 2).[8] Compound **8b**, the *ortho*-fluoro analog of **8a**, was prepared as described above from the allylsulfone (**6b**) because the fluorine should be more readily displaced in the aromatic substitution reaction. Cyclization of **8b** was essentially complete within 24 h and provided **4** in 68% yield. Structural integrity of **4** was confirmed by full NMR assignment.[9]

3. Conclusion

In summary, 1,2,3,4,4a,5-hexahydro-pyrazino[2,1-*c*][1,4]benzothiazine-6,6-dioxide was efficiently prepared by two related approaches. The key reactions involved multistep cascades to form the tricyclic structure.

4. Experimental

4.1. General procedures

General experimental: Solvents and chemicals were purchased from VWR, Oakwood, and Aldrich Chemical Co. and used without further purification. Melting points were obtained on a Thomas–Hoover melting point apparatus and are uncorrected. Chromatography was performed on silica gel, typically using an ISCO Companion. High-resolution mass spectra were typically obtained on a Waters LC-TOFMS instrument and were measured to within 5 ppm of calculated values. ^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired on Bruker DPX (300 MHz), Varian INOVA (400 MHz), and/or Bruker AVANCE II (600 MHz) spectrometers. All 2D NMR data for **4** were acquired on a Bruker AVANCE II 600 MHz NMR spectrometer with a 1.7 mm inverse triple resonance cryoprobe (TCI ^{1}H/^{13}C/^{15}N). NMR data are given as delta values (δ) in parts per million, using tetramethylsilane as an internal reference (δ=0 ppm) or $CFCl_3$ as an external reference (δ=0 ppm), as appropriate. For the NMR data peak descriptions app means apparent and br means broad.

4.2. Syntheses

*4.2.1. 1-(Allylsulfonyl)-2-chlorobenzene (**6a**).* Compound **5a** (2.12 g, 10.0 mmol) was treated with a slurry of Na_2SO_3 (2.35 g, 18.7 mmol) and $NaHCO_3$ (1.68 g, 20 mmol) in water (12 mL). The stirred mixture was heated at 100 °C for 1.5 h, then cooled, and treated with tetrabutylammonium bromide (0.200 g, 0.62 mmol) and allyl bromide (4.25 mL, 50 mmol). The mixture was heated at 70 °C for 6 h. The cooled reaction was treated with water (4 mL) and extracted with dichloromethane (2×15 mL). The extracts were dried ($MgSO_4$), concentrated in vacuo and chromatographed on silica gel using 25:75 ethyl acetate/hexanes to afford **6a** as a colorless oil (2.03 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (1H, app dt, *J* 1.1, 7.4 Hz), 7.59–7.54 (2H), 7.46 (1H, m), 5.74 (1H, m), 5.30 (1H, d with fine coupling, *J* 10.3 Hz), 5.25 (1H, dd, *J* 1.1, 18.2 Hz), 4.16 (2H, dd, *J* 1.0, 7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 135.9. 134.7, 132.6, 132.2, 131.7, 127.3, 124.9, 124.2, 58.7 ppm; MS (ES^+): 216.9 (M+H); HRMS: calcd for $C_9H_9ClO_2S$+H^+, 217.0084; found (ESI, $[M+H]^+$), 217.0095. HPLC purity=100%.

*4.2.2. 1-(Allylsulfonyl)-2-fluorobenzene (**6b**).* Compound **5b** (5.84 g, 30.0 mmol) was treated with a slurry of Na_2SO_3 (7.06 g, 56.0 mmol) and $NaHCO_3$ (5.04 g, 60 mmol) in water (40 mL). The stirred mixture was heated at 100–105 °C for 1.5 h, then cooled, and treated with tetrabutylammonium bromide (0.064 g, 0.20 mmol) and allyl bromide (13.0 mL, 150 mmol). The mixture was heated at 70 °C for

16 h. The cooled reaction was treated with water (20 mL) and extracted with dichloromethane (3×20 mL). The extracts were dried ($MgSO_4$), concentrated in vacuo and chromatographed on silica gel using a 0:100 to 30:70 ethyl acetate/hexane gradient to afford **6b** as a waxy white solid (5.76 g, 96%). Mp: 34–35 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (1H, app dt, *J* 1.8, 7.4 Hz), 7.65 (1H, m), 7.33 (1H, app dt, *J* 0.9, 7.7 Hz), 7.24 (1H, app dt, *J* 0.9, 8.4 Hz), 5.78 (1H, m), 5.32 (1H, dd, *J* 0.7, 10.1 Hz), 5.26 (1H, dd, *J* 1.1, 17.0 Hz), 4.03 (2H, d, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$): δ 159.5 (d, *J* 254 Hz), 136.2 (d, *J* 8 Hz), 131.0, 126.2 (d, *J* 14 Hz), 124.9, 124.7 (d, *J* 4 Hz), 124.2, 117.0 (d, *J* 21 Hz), 60.2 (d, *J* 3 Hz) ppm; ^{19}F{^{1}H} NMR ($CDCl_3$): δ −108.86 ppm; MS (ES^+): 201.0 (M+H); HRMS: calcd for $C_9H_9FO_2S+Na^+$, 223.0200; found (ESI, $[M+Na]^+$), 223.0195. HPLC purity=100%.

*4.2.3. (E)-1-Chloro-2-(3-chloroprop-1-enylsulfonyl)benzene (**7**).* A stirred mixture of $PdCl_2$ (0.049 g, 0.030 mmol), $CuCl_2$ (7.37 g, 54.8 mmol), and NaCl (6.94 g, 119 mmol) in glacial acetic acid (40 mL) was heated at 80 °C for 1 h, then treated with **6a** (1.98 g, 9.14 mmol) and heating continued for 48 h. The dark reaction was cooled, poured into water (100 mL), and extracted with dichloromethane (100 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to an oil, which was chromatographed (silica gel, 40:60 ethyl acetate/hexanes) to afford a 60:40 mixture of **6a** and **7** as a colorless oil (1.95 g). Repeated chromatography gave some clean **7** (0.67 g, 29%) along with mixed **6a** and **7**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (1H, dd, *J* 1.6, 7.8 Hz), 7.60–7.53 (2H), 7.48 (1H, app dt, *J* 1.7, 7.2 Hz), 7.17 (1H, app dt, *J* 5.2, 14.7 Hz), 6.88 (1H, dt, *J* 1.7, 14.7 Hz), 4.26 (2H, dd, *J* 1.7, 5.2 Hz); ^{13}C NMR ($CDCl_3$): δ 142.8, 137.3, 134.9, 132.9, 132.0, 131.5, 131.0, 127.5, 41.4 ppm; MS (ES^-): 249.0 $[M-H]^-$; HRMS: calcd for $C_9H_8Cl_2O_2S-H^-$, 248.9549; found (ESI, $[M-H]^-$), 248.9522. HPLC purity=97.2%.

*4.2.4. 1-Chloro-2-[(2,3-dibromopropyl)sulfonyl]benzene (**8a**).* To a stirred solution of **6a** (5.23 g, 24.1 mmol) in dichloromethane (30 mL) at rt was added drop wise a solution of bromine (4.25 g, 26.6 mmol) in dichloromethane (30 mL) over 10 min. After 4 h, the reaction was concentrated in vacuo to a viscous oil, which solidified. Compound **8a** was isolated as a slightly orange solid (9.03 g, 99%) and used without further purification. Mp: 79–81 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (1H, app dt, *J* 1.9, 7.9 Hz), 7.65–7.58 (2H), 7.51 (1H, app t, *J* 7.4 Hz), 4.57 (1H, m), 4.26 (1H, dd, *J* 5.3, 14.9 Hz), 4.01 (1H, app t, *J* 7.5 Hz), 3.95 (1H, m), 3.74 (1H, dd, *J* 7.5, 11.0 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 136.6, 135.4, 133.0, 132.1, 131.8, 127.6, 59.4, 40.7, 36.0 ppm; MS (ESI^+): 391.9 $[M+NH_4]^+$; HRMS: calcd for $[C_9H_9Br_2ClO_2S+NH_4]^+$, 391.8717; found (ESI, $[M+NH_4]^+$), 391.8737. HPLC purity=100%.

*4.2.5. 1-(2,3-Dibromopropylsulfonyl)-2-fluorobenzene (**8b**).* To a stirred solution of **6b** (5.25 g, 26.2 mmol) in dichloromethane (25 mL) at rt was added drop wise a solution of bromine (1.49 mL, 28.8 mmol) in dichloromethane (25 mL) over about 5 min. After 3 h, the reaction was concentrated in vacuo to a viscous oil, which mostly solidified. The product mass was broken up and triturated with hexanes, then placed under vacuum. Compound **8b** was isolated as a very pale orange solid (9.43 g, 100%) and used without further purification. Mp: 53–55 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (1H, app dt, *J* 1.8, 7.4 Hz), 7.70 (1H, m), 7.38 (1H, app dt, *J* 0.9, 7.8 Hz), 7.28 (1H, app dt, *J* 0.8, 8.4 Hz), 4.55 (1H, m), 4.17 (1H, dd, *J* 5.3, 15.2 Hz), 3.94 (1H, dd, *J* 4.3, 11.1 Hz), 3.85 (1H, dd, *J* 7.3, 15.2 Hz), 3.74 (1H, dd, *J* 7.5, 11.1 Hz); ^{13}C NMR ($CDCl_3$): δ 159.7 (d, *J* 255), 136.9 (d, *J* 4 Hz), 130.6, 127.1 (d, *J* 15 Hz), 125.0 (d, *J* 4 Hz), 117.4 (d, *J* 20 Hz), 60.7, 40.6, 35.9 ppm; ^{19}F{^{1}H} NMR ($CDCl_3$): δ −108.27 ppm; MS (EI): 358.9 $[M]^+$; HPLC purity=96.4%.

*4.2.6. 1,2,3,4,4a,5-Hexahydro-pyrazino[2,1-c][1,4]benzothiazine-6,6-dioxide (**4**).* Compound **7** (251 mg, 1.00 mmol) was dissolved in 2-ethoxyethanol (10 mL) at rt under nitrogen. The reaction was treated with ethylenediamine (201 μL, 3.00 mmol). After 1 h, the reaction was heated at 130–135 °C. After 48 h, the reaction was concentrated in vacuo, treated with satd aq $NaHCO_3$ (5 mL) and brine (2 mL) and extracted with 1:4 ethanol/dichloromethane (3×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography eluting with a 100:0 to 20:80 ethyl acetate/1:9 concd NH_4OH in ethanol gradient afforded the free amine as a slightly yellow oil, partly solidifying after reconcentration from ethanol/water and vacuum drying (171 mg). The material was dissolved in acetonitrile (5 mL), treated with 2 M aqueous HCl (0.60 mL), and concentrated in vacuo to give **4** hydrochloride as an off-white solid (195 mg, 71% from **7**). Mp: 297–299 °C (dec, darkens prior to melting). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.26 (2H, br s), 7.66 (1H, dd, *J* 1.6, 7.9 Hz), 7.52 (1H, app dt, *J* 1.6, 7.2 Hz), 7.26 (1H, d, *J* 8.7 Hz), 6.97 (1H, app t, *J* 7.5 Hz), 4.27 (1H, d, *J* 13.5 Hz), 4.09 (1H, app tt, *J* 3.0, 11.2 Hz), 3.83 (1H, dd, *J* 3.3, 14.1 Hz), 3.56 (1H, dd, *J* 11.3, 14.1 Hz), 3.43–3.44 (2H), 3.23 (1H, app dt, *J* 2.5, 13.1 Hz), 3.06 (2H, app t, *J* 12.0 Hz); MS (ES^+): 239.1 $[M+H]^+$; HRMS: calcd for $C_{11}H_{14}N_2O_2S+H^+$, 239.0849; found (ESI, $[M+H]^+$), 239.0854. HPLC purity=99.9%.

Another sample of free amine **4** was treated with an excess of trifluoroacetic acid and concentrated in vacuo, then reconcentrated from acetonitrile and triturated to afford an off-white solid. Mp: 228–229 °C (dec, gas evolution). HPLC purity=99.1%. The ^{1}H NMR (400 MHz) spectrum was essentially identical to that reported in the literature.[2d]

*4.2.7. 1,2,3,4,4a,5-Hexahydro-pyrazino[2,1-c][1,4]benzothiazine-6,6-dioxide (**4**).* A stirred solution of **8a** (376 mg, 1.00 mmol) in 2-ethoxyethanol (10 mL) under nitrogen was treated with ethylenediamine (267 μL, 4.00 mmol) at rt. After 1 h, the reaction was heated to reflux (135 °C) and maintained at reflux for 48 h. The reaction was cooled and treated with satd aq $NaHCO_3$ (5 mL) and half-saturated brine (5 mL) and then extracted with 1:4 ethanol/dichloromethane (3×15 mL). The dried ($MgSO_4$) extracts were concentrated in vacuo and purified by silica gel chromatography eluting with a 100:0 to 20:80 ethyl acetate/1:9 concd NH_4OH in ethanol gradient to afford a partially solidified yellow oil (180 mg after vacuum drying). This residue was dissolved in acetonitrile (ca. 5 mL) and treated with 2 M aqueous HCl (0.6 mL). The mixture was concentrated in vacuo and dried under vacuum to give **4** hydrochloride as a pale yellow solid (207 mg, 75%). Mp: 297–299 °C (dec, darkens prior to melting). This sample had essentially identical MS and ^{1}H NMR spectra compared to the previous hydrochloride example. HRMS: calcd for $C_{11}H_{14}N_2O_2S+H^+$, 239.0849; found (ESI, $[M+H]^+$), 239.0852. HPLC purity=99.7%.

*4.2.8. 1,2,3,4,4a,5-Hexahydro-pyrazino[2,1-c][1,4]benzothiazine-6,6-dioxide (**4**).* A stirred solution of **8b** (1.08 g, 3.00 mmol) in 2-ethoxyethanol (30 mL) at rt under nitrogen was treated with ethylenediamine (0.80 mL, 12.0 mmol). After 1 h, the reaction was heated to 130 °C for 23 h, then cooled and concentrated in vacuo. The residue was treated with satd aq $NaHCO_3$ (10 mL) and water (5 mL) and then extracted with 1:4 ethanol/dichloromethane (3×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel eluting with a gradient of 0:100 to 25:75 10% concd NH_4OH in ethanol/ethyl acetate gave the free amine as an oil, partly solidifying (ca. 543 mg), which was dissolved in ethanol (or acetonitrile) and treated with 2 M aqueous HCl (1.15 mL) causing precipitation. Concentration in vacuo and reconcentration from water followed by trituration with acetonitrile and suction filtration gave **4** hydrochloride as an off-white solid (496 mg, 60%) and a second crop (63 mg, 8%) as a slightly orange solid. Mp: 297–299 °C (dec, darkens prior to melting). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.90 (2H, br s), 7.66 (1H, dd, *J* 1.7, 7.8 Hz), 7.52 (1H, ddd, *J* 1.8, 7.2, 8.8 Hz), 7.26 (1H, d, *J*

8.7 Hz), 6.97 (1H, t, *J* 7.4 Hz), 4.27 (1H, d, *J* 13.6 Hz), 4.13 (1H, app tt, *J* 3.0, 11.3 Hz), 3.84 (1H, dd, *J* 3.3, 14.1 Hz), 3.57 (1H, dd, *J* 11.3, 14.3 Hz), 3.50–3.41 (2H), 3.27 (1H, app dt, *J* 2.7, 13.1 Hz), 3.10–3.01 (2H); ^{13}C NMR (DMSO-d_6, 151 MHz): δ 145.0, 134.8, 125.4, 124.1, 119.2, 116.6, 52.3, 49.5, 45.8, 44.4, 42.9 ppm; ^{15}N NMR (DMSO-d_6, 61 MHz, indirectly detected by ^{1}H-^{15}N HMBC): δ 73.1, 39.5 ppm (liq. NH_3 δ=0 ppm); MS (ES^+): 239.1 $[M+H]^+$; HRMS: calcd for $C_{11}H_{14}N_2O_2S+H^+$, 239.0849; found (ESI, $[M+H]^+$), 239.0847. HPLC purity=100%.

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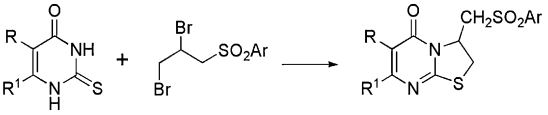

9. Full NMR assignment included ^{1}H NMR, ^{13}C NMR, selective ^{1}H–^{1}H NOESY1D and homonuclear decoupling experiments, as well as ^{1}H–^{13}C HSQC, ^{1}H–^{13}C 1,1-ADEQUATE, ^{1}H–^{13}C HMBC, and ^{1}H–^{15}N HMBC.