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Research Article

Synthesis of [2′-(N-Ethylamino)-5′-Alkyl]phenyl-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone Derivatives by the Proton-Catalyzed Rearrangement of Corresponding Sulfonamides

Anamika Sharma, Sonika Jain, Reenu Sirohi, and D. Kishore

Department of Chemistry, Banasthali University, Banasthali, Rajasthan 304022, India

Correspondence should be addressed to Sonika Jain, sonikajain85@gmail.com

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Synthesis of a new series of heteroaryl sulfones **6(a–f)** in which the heteroaryl part is represented by acridine derivatives has been developed and reported here. The key step of this transformation involves the proton-catalyzed rearrangement of the sulphonamide derivatives **5(a–f)** to the corresponding sulfones **6(a–f)**.

1. Introduction

Chemotherapeutic importance of the sulfonamides, sulfones, and aminosulfones is well known in plethora of diseases [1–12]. Sulfonamides and sulfones have been extensively used in the treatment of leprosy, trachoma, malaria, taxoplasma, and so forth [5–10]. Recent discovery of diaryl sulfones as nonnucleoside reverse transcriptase inhibitors has further aroused our interest in these molecules from yet another perspective [11, 12]. Acridines are endowed with a wide array of pharmacological properties including anticancer, antitumor, antiviral, antimicrobial, antimalarial, analgesic, and anti-inflammatory [13–24]. In view of impressive pharmacodynamic properties exhibited by acridine derivatives, it was considered of interest to synthesize the heteroaryl sulfones containing acridine nucleus as a heteroaryl part in their molecules.

Sulfuric acid has been known to cause rearrangement or hydrolysis of arylsulfonamides [25]. Hydrolysis is the predominant reactions for sulfonamides, while either hydrolysis or rearrangement, depending on acid concentration, is possible for N-substituted sulfonanilides. This reaction has been reinvestigated with a novel view to expand its utility as a synthetic tool for the preparation of several new heteroaryl sulfones.

Present paper describes its application to the synthesis of [2′-(N-ethylamino)-5′-alkyl]phenyl-5,6,7,8-tetrahydroacridine-9-carboxy-2-sulfone derivatives **6(a–f)** from corresponding sulfonamides **5(a–f)**.

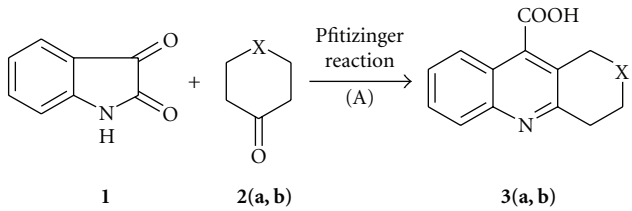
2. Results and Discussion

The acridine derivatives **3(a, b)** were required as key intermediates in the synthesis of heteroaryl sulfonamides **5(a–f)**. These were obtained from isatin (**1**) and **2(a, b)** using the Pfitzinger reaction in accordance with the procedure reported in the literature [26] (Scheme 1).

Chlorosulfonation of **3(a, b)** gave the corresponding sulfonyl chloride **4(a, b)** (Scheme 2).

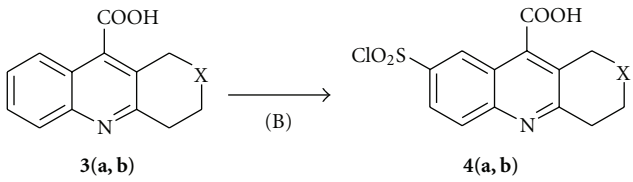
Treatment of **4(a, b)** in the subsequent step with aryl amines followed by reaction with ethyliodide furnished the N-ethylsulfonamides **5(a–f)** (Scheme 3).

N-ethyl sulfonamides have been known to undergo proton-catalyzed rearrangement to the corresponding sulfones [27]. The same methodology when applied on sulfonamides



(a) X = CH_2
(b) X = N–CH_2–C_6H_5

Scheme 1: (A) Aq. EtOH, KOH, reflux.



Scheme 2: (B) $ClSO_3H$, stirring.

5(a–f) yielded the sulfones **6(a–f)** in moderate-to-good yield (Scheme 4).

3. Experimental Section

3.1. General Procedures. Melting points were determined in open glass capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel "G" plates. IR spectra were recorded on CE (SIMADZU) FTIR-8400S. ^{1}HNMR spectra were recorded on model Avance 300 (Bruker 300 MHz) using DMSO-d_6 as a solvent and TMS as an internal reference.

3.2. Materials. Chlorosulfonic acid, cyclohexanone, N,N-dimethyl formamide, N-benzyl piperidone. Cyclohexanone was redistilled and dried prior to use.

*3.3. 5,6,7,8-Tetrahydroacridine-9-Carboxylic Acid (**3a**).* A mixture of isatin (**1**) (1.47 g, 0.01 mol) and **2** (0.98 mL, 0.01 mol) in 50% aq. EtOH (15 mL) containing KOH (3 g) was heated under reflux for 4 h. Reaction mixture was diluted with 50% aq. EtOH to obtain homogeneous mixture and acidified with AcOH. Resulting precipitate was collected, washed with aq. EtOH, and recrystallized from DMF to give **3a**, 1.7 g (yield 75%), m.p. 284-285°C. IR (KBr): 2998 (O–H) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 8.20 (1H, d, H_{arom}), 7.98 (2H, m, H_{arom}), 7.89 (1H, t, H_{arom}), 3.05 (2H, t, CH_2), 2.76 (2H, t, CH_2), 1.79 (4H, m, CH_2). Anal. Calcd. for $C_{14}H_{13}NO_2$ (277.25): C, 73.49; H, 5.27; N, 5.66. Found: C, 73.99; H, 5.77; N, 6.16.

Similarly compound **3b** was prepared by the similar method with required change in reflux time.

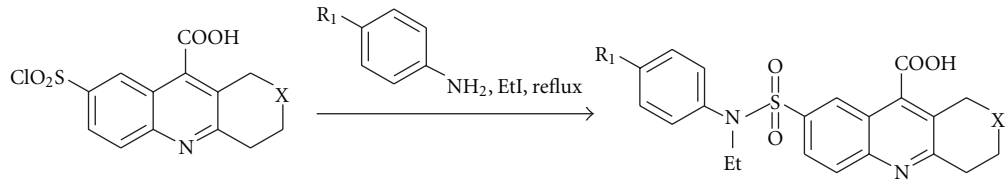
*3.4. 7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxylic Acid (**3b**).* Yield 69%; m.p. 290-291°C. IR (KBr): 3000 (O–H) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 8.20 (1H, d, H_{arom}), 7.98 (2H, m, H_{arom}), 7.89 (1H, t, H_{arom}), 7.33 (2H, m, H_{arom}), 7.26 (1H, t, H_{arom}), 7.23 (2H, d, H_{arom}), 3.70 (2H, s, CH_2), 3.66 (2H, s, CH_2), 3.09 (2H, t, CH_2), 2.73 (2H, t, CH_2). Anal. Calcd. for $C_{20}H_{18}N_2O_2$(318.36): C, 75.02; H, 5.53; N, 8.30. Found: C, 75.45; H, 5.70; N, 8.80.

*3.5. 5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonylchloride (**4a**).* Compound **3a** (1.13 g, 0.005 mmol) was added in portion wise to chlorosulfonic acid (10 mL). The reaction mixture was stirred at room temperature for 1 h and then at 50–60°C for 5 h. Mixture was poured into crushed ice, and the resulting precipitate was filtered off, washed with water, and dried in vacuum. The product was recrystallized from ethanol to give **4a**, 1.15 g (yield 70%), m.p. 269-270°C. IR (KBr): 2900 (O–H) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.77 (1H, s, H_{arom}), 8.49 (1H, d, H_{arom}), 8.43 (1H, d, H_{arom}), 3.05 (2H, t, CH_2), 2.76 (2H, t, CH_2), 1.79 (4H, m, CH_2). Anal. Calcd. for $C_{14}H_{12}ClNO_4S$ (325.76): C, 51.12; H, 3.31; N, 3.80; S, 9.33. Found: C, 51.62; H, 3.71; N, 4.30; S, 9.84.

Similarly compound **4b** was prepared by using appropriate reactants.

*3.6. 7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonylchloride (**4b**).* Yield 68%; m.p. 283-284°C. IR (KBr): 2990 (O–H) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.77 (1H, s, H_{arom}), 8.49 (1H, d, H_{arom}), 8.43 (1H, d, H_{arom}), 7.33 (2H, m, H_{arom}), 7.26 (1H, t, H_{arom}), 7.23 (2H, d, H_{arom}), 3.70 (2H, s, CH_2), 3.66 (2H, s, CH_2), 3.09 (2H, t, CH_2), 2.73 (2H, t, CH_2). Anal. Calcd. for $C_{20}H_{17}ClN_2O_4S$ (416.87): C, 57.12; H, 3.61; N, 6.21; S, 7.17. Found: C, 57.62; H, 4.11; N, 6.72; S, 7.69.

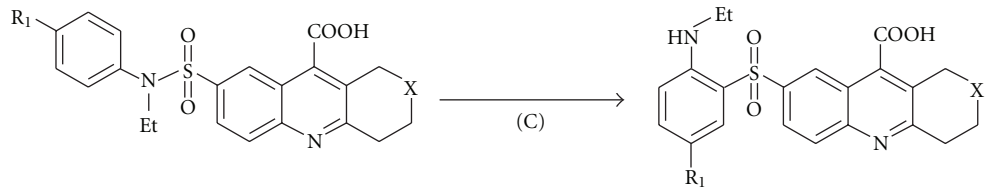
*3.7. [N-Ethyl-N-(4′-Methylphenyl)]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5a**).* To a solution of compound **4a** (1.6 g, 0.005 mmol) and p-toluidine (0.5 g, 0.005 mmol) in ethanol (10 mL), a pinch of $NaHCO_3$ was added and the reaction mixture was refluxed for 2 h on a water bath. It was then poured into ice and the precipitate was filtered, washed with water, and dried in vacuum to get sulphonamide. This sulfonamide (1.9 g, 0.005 mmol) was mixed with aq. KOH (1 g in 10 mL water) and then heated to 70°C. Iodoethane (5 mL) was added dropwise over 1 hr. After this period, the ethyl compound began to separate. Heating was continued for further 2 hr. The reaction mixture was allowed to cool, the solid, which separated, was recrystallized from ethanol to give pure compound **5a**, 1.5 g (yield 70%), m.p. 204-205°C. IR (KBr): 1650 (C=O), 2995 (O–H), 1300, 1150 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.48 (2H, d, H_{arom}), 3.20 (2H, q, CH_2), 3.05 (2H, t, CH_2), 2.76 (2H, t, CH_2), 2.35 (3H, s, CH_3), 1.79 (4H, m, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{23}H_{24}N_2O_4S$ (424.51): C, 64.57; H, 5.30; N, 6.10; S, 7.05. Found: C, 65.07; H, 5.70; N, 6.60; S, 7.55.



4(a, b) **5(a–f)**

(a) $R_1 = CH_3$, X = CH_2
(b) $R_1 = OCH_3$, X = CH_2
(c) $R_1 = OC_2H_5$, X = CH_2
(d) $R_1 = CH_3$, X = –N–CH_2–C_6H_5
(e) $R_1 = OCH_3$, X = –N–CH_2–C_6H_5
(f) $R_1 = OC_2H_5$, X = –N–CH_2–C_6H_5

Scheme 3



5(a–f) **6(a–f)**

Scheme 4: (C) H_2SO_4.

Compound **5(b–f)** were prepared by the similar method using appropriate reactants with required change in reflux time.

*3.8. [N-Ethyl-N-(4′-Methoxyphenyl)]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5b**).* Yield 71%; m.p. 217-218°C. IR (KBr): 1690 (C=O), 2980 (O–H), 1310, 1105 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.48 (2H, d, H_{arom}), 3.83 (3H, s, CH_3), 3.20 (2H, q, CH_2), 3.05 (2H, t, CH_2), 2.76 (2H, t, CH_2), 1.79 (4H, m, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{23}H_{24}N_2O_5S$ (440.51): C, 62.34; H, 5.09; N, 5.86; S, 6.78. Found: C, 62.71; H, 5.49; N, 6.36; S, 7.28.

*3.9. [N-Ethyl-N-(4′-Ethoxyphenyl)]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5c**).* Yield 70%; m.p. 212-213°C. IR (KBr): 1716 (C=O), 2985 (O–H), 1309, 1100 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.48 (2H, d, H_{arom}), 4.09 (2H, q, CH_2), 3.20 (2H, q, CH_2), 3.05 (2H, t, CH_2), 2.76 (2H, t, CH_2), 1.79 (4H, m, CH_2), 1.32 (3H, t, CH_3), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{24}H_{26}N_2O_5S$ (454.53): C, 63.12; H, 5.47; N, 5.66; S, 6.55. Found: C, 63.42; H, 5.77; N, 6.16; S, 7.05.

*3.10. [N-Ethyl-N-(4′-Methylphenyl)]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5d**).* Yield 69%; m.p. 224-225°C. IR (KBr): 1700 (C=O), 2910 (O–H), 1300, 1101 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.33 (2H, m, H_{arom}), 7.26 (1H, t, H_{arom}), 7.23 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.48 (2H, d, H_{arom}), 3.70 (2H, s, CH_2), 3.26 (2H, q, CH_2), 3.09 (2H, s, CH_2), 2.78 (2H, t, CH_2), 2.34 (3H, s, CH_3), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{29}H_{29}N_3O_4S$ (515.62): C, 67.35; H, 5.27; N, 7.64; S, 5.72. Found: C, 67.55; H, 5.67; N, 8.15; S, 6.22.

*3.11. [N-Ethyl-N-(4′-Methoxyphenyl)]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5e**).* Yield 70%; m.p. 243-244°C. IR (KBr): 1720 (C=O), 2885 (O–H), 1301, 1119 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.33 (2H, m, H_{arom}), 7.26 (1H, t, H_{arom}), 7.23 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.77 (2H, d, H_{arom}), 3.83 (3H, s, CH_3), 3.70 (2H, s, CH_2), 3.26 (2H, q, CH_2), 3.09 (2H, s, CH_2), 2.78 (2H, t, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{29}H_{29}N_3O_5S$ (531.62): C, 65.02; H, 5.12; N, 7.40; S, 5.52. Found: C, 65.52; H, 5.50; N, 7.90; S, 6.03.

*3.12. [N-Ethyl-N-(4′-Ethoxyphenyl)]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfonamide (**5f**).* Yield 68%; m.p. 253-254°C. IR (KBr): 1702 (C=O), 2985 (O–H), 1310, 1105 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.76 (1H, s, H_{arom}), 8.48 (2H, d, H_{arom}), 7.33 (2H, m, H_{arom}), 7.26 (1H, t, H_{arom}), 7.23 (2H, d, H_{arom}), 7.01 (2H, d, H_{arom}), 6.77 (2H, d, H_{arom}), 4.09 (2H, q, CH_2), 3.70 (2H, s, CH_2), 3.26 (2H, q, CH_2), 3.09 (2H, s, CH_2), 2.78 (2H, t,

CH_2), 1.32 (3H, t, CH_3), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{30}H_{31}N_3O_5S$ (545.64): C, 65.84; H, 5.33; N, 7.20; S, 5.38. Found: C, 66.04; H, 5.73; N, 7.70; S, 5.88.

*3.13. [(2′-(N-Ethylamino)-5′-Methyl)phenyl]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6a)**.* Compound **5a** (2.1 g, 0.005 mmol) was dissolved in H_2SO_4 (A.R.10 mL). After acquiring dark brown colour, it was cooled and poured dropwise into ice cold water. Resulting precipitate was filtered, washed with water, and recrystallized from ethanol to give pure compound **6a**, 1.61 g (yield 70%), m. p. 266-267°C. IR (KBr): 3386 (NH), 3000 (O–H), 1658 (C=O), 1303, 1157 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom}), 8.45 (2H, s, H_{arom}), 7.48 (1H, s, H_{arom}), 6.8 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.10 (2H, q, CH_2), 2.88 (2H, t, CH_2), 2.55 (2H, t, CH_2), 2.35 (3H, s, CH_3), 1.62 (4H, m, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{23}H_{24}N_2O_4S$ (424.51): C, 64.57; H, 5.30; N, 6.10; S, 7.05. Found: C, 65.07; H, 5.70; N, 6.60; S, 7.55.

Compound **6(b–f)** were prepared by the similar method using appropriate reactants.

*3.14. [(2′-(N-Ethylamino)-5′-Methoxy)Phenyl]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6b)**.* Yield 72%; m.p. 273-274°C. IR (KBr): 3417 (NH), 2981 (O–H), 1700 (C=O), 1300, 1155 (S=O) cm^{-1};^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom}), 8.45 (2H, s, H_{arom}), 7.19 (1H, s, H_{arom}), 6.6 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.73 (3H, s, CH_3), 3.10 (2H, q, CH_2), 2.88 (2H, t, CH_2), 2.55 (2H, t, CH_2), 1.62 (4H, m, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{23}H_{24}N_2O_5S$ (440.51): C, 62.34; H, 5.09; N, 5.86; S, 6.78. Found: C, 62.71; H, 5.49; N, 6.36; S, 7.28.

*3.15. [(2′-(N-Ethylamino)-5′-Ethoxy)Phenyl]-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6c)**.* Yield 73%; m.p. 263-264°C. IR (KBr): 3400 (NH), 2995 (O–H), 1710 (C=O), 1301, 1156 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom},), 8.45 (2H, s, H_{arom}), 7.19 (1H, s, H_{arom}), 6.6 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.98 (2H, q, CH_2), 3.10 (2H, q, CH_2), 2.88 (2H, t, CH_2), 2.55 (2H, t, CH_2), 1.62 (4H, m, CH_2), 1.33 (3H, t, CH_3), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{24}H_{26}N_2O_5S$ (454.53): C, 63.12; H, 5.47; N, 5.66; S, 6.55. Found: C, 63.42; H, 5.77; N, 6.16; S, 7.05.

*3.16. [(2′-(N-Ethylamino)-5′-Methyl)Phenyl]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6d)**.* Yield 70%; m.p. 251-252°C. IR (KBr): 3396 (NH), 2900 (O–H), 1700 (C=O), 1319, 1150 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom}), 8.45 (2H, s, H_{arom}), 7.48 (1H, s, H_{arom}), 7.06–7.14 (5H, m, H_{arom}), 6.8 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.62 (4H, s, CH_2), 3.10 (2H, q, CH_2), 2.98 (2H, t, CH_2), 2.69 (2H, t, CH_2), 2.35 (3H, s, CH_3), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{29}H_{29}N_3O_4S$ (515.62): C, 67.35; H, 5.27; N, 7.64; S, 5.72. Found: C, 67.55; H, 5.67; N, 8.15; S, 6.22.

*3.17. [(2′-(N-Ethylamino)-5′-Methoxy)Phenyl]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6e)**.* Yield 71%; m.p. 257-258°C. IR (KBr): 3390 (NH); 2895 (O–H), 1705 (C=O), 1315, 1145 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom}), 8.45 (2H, s, H_{arom}), 7.19 (1H, s, H_{arom}), 7.06–7.14 (5H, m, H_{arom}), 6.6 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.73 (3H, s, CH_3), 3.62 (4H, s, CH_2), 3.10 (2H, q, CH_2), 2.98 (2H, t, CH_2), 2.69 (2H, t, CH_2), 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{29}H_{29}N_3O_5S$ (531.62): C, 65.02; H, 5.12; N, 7.40; S, 5.52. Found: C, 65.52; H, 5.50; N, 7.90; S, 6.03.

*3.18. [(2′-(N-Ethylamino)-5′-Methoxy)Phenyl]-7-(N-Benzyl)-5,6,7,8-Tetrahydroacridine-9-Carboxy-2-Sulfone **(6f)**.* Yield 70%; m.p. 279-280°C. IR (KBr): 3385 (NH); 2990 (O–H), 1670 (C=0), 1326, 1140 (S=O) cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 11.0 (1H, s, COOH), 9.73 (1H, s, H_{arom}), 8.45 (2H, s, H_{arom}), 7.19 (1H, s, H_{arom}), 7.06–7.14 (5H, m, H_{arom}), 6.6 (1H, d, H_{arom}), 6.48 (1H, d, H_{arom}), 4.0 (1H, s, NH), 3.98 (2H, q, CH_2), 3.62 (4H, s, CH_2), 3.10 (2H, q, CH_2), 2.98 (2H, t, CH_2), 2.69 (2H, t, CH_2), 1.33 (3H, t, CH_3) 1.13 (3H, t, CH_3). Anal. Calcd. for $C_{30}H_{31}N_3O_5S$ (545.64): C, 65.84; H, 5.33; N, 7.20; S, 5.38. Found: C, 66.04; H, 5.73; N, 7.70; S, 5.88.

4. Conclusion

In conclusion, sulphones were prepared by commercially available isatin, cyclohexanone, and N-benzyl-4-piperidone. We can conclude that proton-catalyzed rearrangement of sulfonamides provides a versatile method for the preparation of corresponding sulfones.

Acknowledgments

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