Synthesis and hypoglycemic activity of 5,5-dimethylarylsulfonylimidazolidine-2,4-diones

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Abstract

1-Arylsulfonyl-5,5-dimethylimidazolidine-2,4-diones (**3a-d**) were prepared by the rearrangement of 3-arylsulfonyl-5,5-dimethylimidazolidine-2,4-diones (**2a-d**). Compounds (**2a-d**) were in turn synthesized by the reaction of arylsulfonyl chlorides with 5,5-dimethylimidazolidine-2,4-dione. All the synthesized compounds were characterized by modern spectroscopic techniques. Two of the synthesized compounds, (**2a**) and (**3a**), proved to be the stimulators of insulin release when used at concentrations of 100 μM.

Keywords: Imidazolidinediones, hypoglycemic, sulfonylurea

Introduction

Diabetes is one of the major killers of our time, with people in South-east Asia and Western Pacific being the most at risk.[1] To cure the disease and the associated complications, sulfonyl ureas are the most frequently used antidiabetic drugs, known to reduce the HbA1c levels by 1.5 to 2.0 percent and fasting plasma glucose (FPG) levels by 54 to 72 mg per dL.[2-4] The N-arylsulfonylimidazolidine-2,4-diones have, in addition to the sulfonyl moiety, a urea core afforded by the imidazolidine-2,4-dione ring and fulfill all the requirements suggested in the pharmacophoric models for maximum hypoglycemic activity[5] and treatment of hypoglycemic complications.[6] Sulfonylimidazolidine-2,4-diones have previously been reported as antidiabetic agents in general and aldose reductase inhibitors in particular.[7,8] It has also been reported[9] that imidazolidine-2,4-diones with arylsulfonyl group at position one are more active than their counterparts with substitution at position three. A number of other bioactivities are also associated with the imidazolidien-2,4-dione nucleus itself.[10-12]

As a continuation of our previous work on the synthesis of arylsulfonylimidazolidine-2,4-diones[13,14] and arylsulfonylbenzimidazolone derivatives[15] and their evaluation as hypoglycemic agents, we have synthesized 3-arylsulfonylimidazolidine-2,4-diones **(2a-d)** and rearranged to 1-arylsulfonylimidazolidine-2,4-diones **(3a-d)** in presence of sodium hydride **(Figure 1)**. The

structures of all the synthesized compounds were established by modern spectroscopic techniques and purity ascertained by elemental analysis. The *in vitro* hypoglycemic activity of two of the compound **(2a** and **3a)** is also being reported.

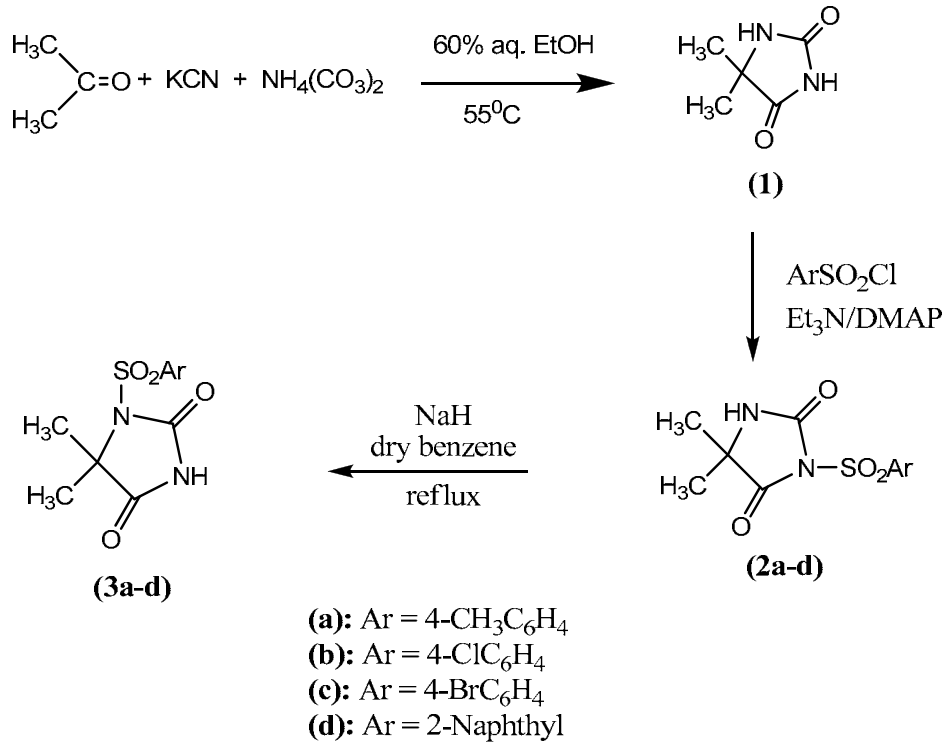

Figure 1. Synthesis of 1-arylsulfonylimidazolidine-2,4-diones.

Results and Discussion

Synthesis

3-Arylsulfonylimidazolidine-2,4-diones **(2a-d)** were synthesized by the reaction of 5,5-dimethylimidazolidine-2,4-dione **(1)** with aryl sulfonyl chlorides in the presence of triethylamine.[16] The 5,5-dimethylimidazolidine-2,4-dione **(1)** itself was prepared by a standard procedure.[17] The synthesis of 3-arylsulfonylimidazolidine-2,4-diones **(2a-d)** was indicated in the IR spectra by the appearance of the absorptions for anti-symmetric and symmetric O=S=O stretchings in the narrow ranges of 1359-1357 cm^{-1} and 1168-1148 cm^{-1}. The synthesis of **2a-d** was confirmed in the ^{1}H-NMR spectra by the presence of only one broad signal for –NH absorptions in the range 8.35 to 8.12 ppm. The non-observance of the signal in the range of 10.00 – 9.00 ppm indicated that the more acidic proton has been substituted. The appearance of signals in the aromatic region also confirmed the synthesis. In the mass spectra, the loss of 64 mass units, corresponding to SO_2, was a common observation. The base peak in all the

compounds was observed at m/z 85. For compounds **2b** and **2c** characteristic isotope peaks were also observed.

The rearrangement of 3-arylsulfonylimidazolidine-2,4-diones **(2a-d)** in presence of sodium hydride[18] afforded 1-arylsulfonylimidazolidine-2,4-diones **(3a-d)**. The rearrangement to **3a-d** was confirmed in the ^{1}H-NMR spectra by appearance of the –NH signal in the region 10.30 – 9.33 ppm. This position of absorption strongly suggests that the more acidic proton is now free and the arylsulfonyl group has migrated to position 1. The mass spectral results were also in accordance with the proposed structures.

Antidiabetic activity

The ability of two of these 5,5-Dimethylarylsulfonylimidazolidine-2,4-diones namely; 5,5-dimethyl-1-(4-methylphenyl)imidazolidine-2,4-dione **(3a)** and 5,5-dimethyl-3-(4-methylphenyl)imidazolidine-2,4-dione **(2a)**, to stimulate insulin release was tested using concentrations of 10 μM and 100 μM. The corresponding concentrations of solvent from the stock solutions were 0.2 or 2 %. At a concentration of 2 %, methanol alone increased insulin release; this value was taken as control for the effect of 100 μM of the test agents. The static incubation of insulin-secreting INS-1 cells revealed that at 100 μM, but not at 10 μM, both test agents affected insulin release **(Table 1)**. The 1-substituted compound, however, achieved only a marginally significant increase because of the large scatter of the data, whereas the 3-substituted compound was clearly effective. Tolbutamide, a classical pharmacological stimulator of insulin secretion belonging to the class of sulfonylurea compounds,[19] stimulated insulin release under the same conditions as used to measure the effect of the test agents. At 800 μM, tolbutamide increased the insulin content in the medium to 16.5 ng/ml which has to be compared with 18.1 ± 1.4 ng/ml achieved by 100 μM of 5,5-dimethyl-3-(4-methylphenyl)imidazolidine-2,4-dione **(2a)**.

Table 1. Effect of test compounds on insulin release by INS-1 cells

Concentration	5,5-dimethyl-1-(4-methylphenyl)imidazolidine-2,4-dione (**3a**)	5,5-dimethyl-3-(4-methylphenyl)imidazolidine-2,4-dione (**2a**)
10 μM	8.1 ± 0.5	8.0 ± 0.3
100 μM	24.0 ± 4.8	18.1 ± 1.4

Insulin release by INS-1 cells during a 1 h incubation at 37 °C. The insulin content of the incubation medium is expressed as ng/ml. All the data is given as mean ± SEM of 3 experiments. The insulin content after control incubation with 0.2 % methanol was 9.3 ± 0.7 ng/ml and with 2 % methanol 13.4 ± 0.6 ng/ml. a) $P = 0.08$, b) $P < 0.05$, in comparison with the effect of 2 % methanol alone (Student's unpaired two-tailed t-test).

Both the test agents proved to be stimulators of insulin release when used at concentrations of 100 μM. Since both compounds were ineffective at 10 μM, their potency is only moderate,

similar to that of tolbutamide, a first generation sulfonylurea. The magnitude of the insulinotropic effect was also similar to that of tolbutamide. From the current data it cannot be decided whether there is difference between the insulinotropic efficiencies of these two isomeric compounds. At any rate, it seems worthwhile to check whether these compounds have essentially the same mechanism of action as the sulfonylureas, *i.e.* closure of ATP-dependent potassium channels, leading to Ca^{2+} influx into the cell and stimulation of secretion, or whether they affect a new therapeutic target.

Incited by these results, the *in vivo* hypoglycemic activities of these and related compounds are underway in this laboratory. Some excellent *in vivo* hypoglycemic results have been obtained and will be published separately.[20]

Experimental Section

General Procedures. Melting points of the compounds were determined in open capillaries using Gallenkemp melting point apparatus and are uncorrected. IR spectra were recorded on a FTS 3000 MX, Bio-Rad Merlin (Excalibur Model) spectrophotometer either as KBr discs while ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrophotometer as acetone-d_6 solutions using TMS as an internal standard. EIMS were measured on a MAT-112-S machine at 70 eV and Elemental analysis was performed on Leco CHNS-932 (USA) Leco Corporation.

Synthesis of 5,5-dimethylimidazolidine-2,4-dione.[17] Acetone (0.1 mol) and ammonium carbonate (0.6 mol) were placed in a 100 ml round bottom flask. Potassium cyanide (0.1 mol), dissolved in ethanol (60%), was added to the flask and the mixture heated on an oil bath at 55-60°C. After completion of the reaction, the mixture was cooled to room temperature and acidified using concentrated HCl. The resulting precipitates were filtered, dissolved in saturated NaOH solution and extracted once with diethyl ether. The ethereal extract was discarded and aqueous layer was acidified to get the precipitates of immidazolidine-2,4-dione. The precipitates were filtered, dried (anhydrous $MgSO_4$) and recrystallized from ethanol/water. The product was pale yellow in colour. Yield: 65%; M.P: 180 °C (lit. 182 °C[17]); IR (KBr, cm^{-1}) 3465, 3278, 2960, 1776, 1665, 1275.

General method for the synthesis of 3-arylsulfonylimidazolidine-2,4-diones[16]

To a well stirred mixture of imidazolidine-2,4-dione (4.8 mmol), triethylamine (4.8 mmol) and catalytic amounts of DMAP, was dropwise added a solution of arylsulfonyl chloride (5.8 mmol) in an appropriate volume of dichloromethane and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was diluted with 1N HCl till pH 2 and extracted with dichloromethane (3 × 25 mL). The crude product after evaporation of the solvent was recrystallized from ethyl acetate to afford a crystalline powder.

5,5-Dimethyl-3-(4-methylphenyl)imidazolidine-2,4-dione (2a). Yield: 76%; Mp. 137 °C; IR (KBr, cm^{-1}) 3477, 3279, 2967, 1694, 1663, 1359, 1278, 1148, 978, 849; ^{1}H NMR (acetone-d_6) δ 1.38 (s, 6H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR (acetone-d_6) δ 24.1, 25.9 , 54.6, 126.3, 129.5, 135.8, 140.2, 161.8, 175.9; MS: *m/z* 218, 217, 203, 172, 155, 127, 91, 65; Anal. Calcd. for $C_{12}H_{14}N_2O_4S$ (282.07): C, 51.05; H, 5.00; N, 9.92; S, 11.36. Found: C, 51.89; H, 5.09; N, 9.82; S, 11.48.

3-(4-Chlorophenylsulfonyl)-5,5-dimethylimidazolidine-2,4-dione (2b). Yield: 56%; Mp. 134 °C; IR (KBr, cm^{-1}) 3468, 3279, 2962, 1693, 1655, 1358, 1262, 1145, 976, 848; ^{1}H NMR (acetone-d_6) δ 1.31 (s, 6 H), 7.73 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR (acetone-d_6) δ 33.3, 56.8, 124.8, 125.6, 137.3, 154.0, 157.9, 182.9; MS: *m/z* 240, 238, 191, 177, 175, 127, 113, 111, 85, 64; Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S$ (302.01): C, 43.64; H, 3.66; N, 9.25; S, 10.59. Found: C, 43.38; H, 3.58, N; 9.53; S, 10.79.

3-(4-Bromophenylsulfonyl)-5,5-dimethylimidazolidine-2,4-dione (2c). Yield: 52%; Mp. 142 °C; IR (KBr, cm^{-1}) 3468, 3264, 2966, 1693, 1663, 1357, 1278, 1163, 973, 844; ^{1}H NMR (acetone-d_6) δ 1.39 (s, 6H), 7.69 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR (acetone-d_6) δ 25.7, 53.3, 122.7, 129.0, 131.9, 150.0, 152.1, 185.9; MS: *m/z* 284, 282, 262, 260, 220, 218, 156, 154, 85; Anal. Calcd. for $C_{11}H_{11}BrN_2O_4S$(345.96): C, 38.05; H, 3.19; N, 8.07; S, 9.24. Found: C, 37.89; H, 3.34; N, 8.26; S, 9.13.

5,5-Dimethyl-3-(naphth-2-ylsulfonyl)imidazolidine-2,4-dione(2d). Yield: 55%; Mp. 197 °C; IR (KBr, cm^{-1}) 3478, 3277, 2963, 1694, 1666, 1357, 1266, 1168, 985, 857; ^{1}H NMR (acetone-d_6) δ 1.39 (s, 6H), 7.75 (m, 7H), 8.28 (s, 1H); ^{13}C NMR (acetone-d_6) δ 25.7, 59.3, 123.2, 126.5, 126.8, 127.2, 127.5, 127.9, 128.0, 129.5, 136.8, 137.6, 165.8, 180.9; MS: *m/z* 254, 191, 127, 85; Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.07): C, 56.59; H, 4.43; N, 8.80; S, 10.07 Found: C, 56.69; H, 4.63; N, 8.65; S, 10.22.

General method for the synthesis of 1-arylsulfonylimidazolidine-2,4-diones[18]

To a solution of 3-arylsulfonylimidazolidine-2,4-dione (0.001 mol) in dry benzene (15 ml), sodium hydride (0.0012 mol) was added and the mixture refluxed under argon atmosphere for two hours. The solvent was evaporated and petroleum ether was added. The sodium salt of 1-arylsulfonylimidazolidine-2,4-dione so precipitated was filtered, dissolved in water, neutralized with IN HCl and extracted with ethyl acetate (3 × 25 mL). After evaporation of the solvent, the rearranged product was recrystallized from ethyl acetate to afford a white crystalline powder.

5,5-Dimethyl-1-(4-methylphenyl)imidazolidine-2,4-dione (3a). Yield: 96%; Mp. 132 °C; IR (KBr, cm^{-1}) 3375, 2908, 2590, 1961, 1733, 1674, 842; ^{1}H NMR (acetone-d_6) δ 1.28 (s, 6H), 1.48 (s, 3H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 10.30 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.3, 23.9, 52.5, 125.3, 128.3, 135.8, 139.8, 155.8, 178.3; MS: *m/z* 282, 218, 197, 155, 85, 65; Anal. Calcd. for $C_{12}H_{14}N_2O_4S$ (282.07): C, 51.05; H, 5.00; N, 9.92; S, 11.36. Found: C, 51.23; H, 5.09; N, 9.86; S, 11.27.

1-(4-Chlorophenylsulfonyl)-5,5-dimethylimidazolidine-2,4-dione (3b). Yield: 93%; Mp. 125 °C IR (KBr, cm^{-1}) 3387, 2955, 2598, 1945, 1740, 1672, 848. ^{1}H NMR (acetone-d_6) δ 1.32 (s,

6H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 2H), 9.33 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.3, 52.8, 126.8, 129.3, 136.8, 155.8, 178.8; MS: *m/z* 304, 302, 240, 238, 218, 216, 177, 175, 85 (100); Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S$ (302.73): C, 43.64; H, 3.66; N, 9.25; S, 10.59. Found: C, 43.56; H, 3.65; N, 9.39; S, 10.42.

1-(4-Bromophenylsulfonyl)-5,5-dimethylimidazolidine-2,4-dione (3c). Yield: 92%; Mp. 136 °C IR (KBr, cm^{-1}): 3378, 2971, 2590, 1940, 1735, 1674, 825; ^{1}H NMR (acetone-d_6) δ 1.39 (s, 6H), 7.49 (d, *J* = 8.7 Hz, 2H), 8.53 (d, *J* = 8.7 Hz, 2H,), 9.35 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.3,53.3, 128.3, 131.9, 125.8, 137.8, 157.8, 177.8; MS: *m/z* 349, 347, 282, 280, 262, 260, 219, 217, 85; Anal. Calcd. for $C_{11}H_{11}BrN_2O_4S$(347.19): C, 38.05; H, 3.19; N, 8.07; S, 9.24. Found: C, 37.94; H, 3.27; N, 8.15; S, 9.09.

5,5-Dimethyl-1-(naphth-2-ylsulfonyl)imidazolidine-2,4-dione (3d). Yield: 86%; Mp. 129 °C; IR (KBr, cm^{-1}) 3371, 2920, 2561, 1963, 1725, 1677, 833; ^{1}H NMR (acetone-d_6) δ 1.23 (s, 6H), 7.88 (m, 7H), 9.88 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.8, 52.5, 122.3, 125.3, 126.3, 127.3, 128.2, 133.2, 136.9, 159.7,178.3; MS: *m/z* 318, 254, 233, 191, 127, 85; Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.07): C, 56.59; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.46; H, 4.58; N, 8.62; S, 10.26.

Measurement of insulin secretion

5,5-Dimethyl-1-(4-methylphenyl)imidazolidine-2,4-dione **(3a)** and 5,5-Dimethyl-3-(4-methylphenyl)imidazolidine-2,4-dione **(2a)** were prepared as a 5 mM stock solution in methanol. Measurement of insulin secretion was performed by static incubation of ca. 0.5 × 10^6 insulin-secreting INS-1 cells in 12-well dishes. The incubation medium was a Krebs-Ringer buffer containing 5 mM glucose. After incubation for 1 h at 37 °C, 500 µl of the incubation medium were aspirated from each well and centrifuged to pellet aspirated cells. Insulin content in the supernatant was determined by a sandwich ELISA according to the instructions of the manufacturer (Mercodia AB, Uppsala, Sweden).

Acknowledgements

The authors are thankful to Rustenbeck I. of the Tech Univ Carolo Wilhelmina Braunschweig, Inst Pharmacol, D-38106 Braunschweig, Germany for the measurements of insulin secretion.

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