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Synthesis, Characterization, and Cytotoxicity of Some New Sulfonylaziridine Derivatives

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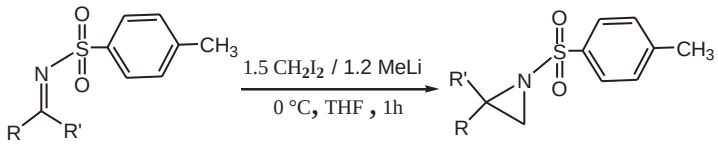
ABSTRACT Some new N-sulfonylaziridine derivatives **(2a-d)** were synthesized by the reaction of sulfonylimines **1** and CH_2I_2 with tetrahydrofuran in the presence of MeLi and diethyl ether at 0°C. The structures of the compounds have been established by means of infrared, proton, and carbon nuclear magnetic resonance.



KEYWORDS Sulfonylimines, Sulfonylaziridines, Cytotoxicity.

INTRODUCTION

Aziridines are nitrogen-containing, three-membered ring heterocycles, which are widely known as useful reactive intermediates in the synthesis of amino acid derivatives, azomethine ylides, or chiral amino alcohols.[1-3] In addition, they are used as chiral auxiliaries and chiral ligands in asymmetric synthesis[4-8] or in fused heterocycles.[9] Besides, their importance as reactive intermediates, aziridine-containing compounds possess many biological activities especially antitumor and antibacterial ones, due to the presence of the aziridine ring.[10] Aziridines are powerful alkylating agents and their *in vivo* potency is based primarily on toxicity rather than specific activity. The toxicity of aziridine derivatives depends on their structure, and several important natural products, such as mitomycin C,[11] porfiromycin,[12] and carzinophilin A.[13]

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded using BRUKER spectrophotometer 400 MHz (University of Isfahan, Iran) and ^{13}C NMR spectra were recorded using BRUKER spectrophotometer 125 MHz. The chemical shift values are expressed in δ ppm using tetramethylsilane as internal standard and using d6-dimethyl sulfoxide (DMSO) as a solvent. Infrared (IR) spectra were recorded KBr on a Shimadzu spectrophotometer and frequencies are presented as cm^{-1}.

General procedure for the synthesis of sulfonylimine (1a-d)[14]

In general, the Schiff bases (mono-bis imines) were prepared by the mixture of aldehyde (4 mmol) and an amine (4 mmol) in ethanol (25 mL) and 2–3 drops of glacial acetic acid for 30 min–48 h. The reaction was followed by thin-layer chromatography (3:7 ethyl acetate/hexane) as eluent. After completion the reaction, the solvent was evaporated and crude product was recrystallized from benzene.

General procedure for the synthesis of sulfonylaziridines (2a-d)[15]

To a mixture of N-sulfonylimine **1** (0.4 mmol) and CH_2I_2 (0.6 mmol, 1.5 eq.) in dry tetrahydrofuran (2 mL), a solution of MeLi in ether was added (1.5 M, 0.48 mmol, 1.2 eq.) at 0°C. The solution was stirred at the same temperature for 30 min and then was left at room temperature for an

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additional 30 min. The reaction mixture was then quenched with NH_4Cl aq. and the organic layer was then extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield crude N-sulfonylaziridines **2**, which were purified by flash chromatography on silica gel (Hexane/EtOAc 10/1).

N,N-Dimethyl-4-(1-tosylaziridin-2-yl)aniline (2a)

It was prepared by reacting N-(4-(dimethylamino) benzylidene)-4-methylbenzenesulfonamide (0.002 mol, 0.8 g) with diiodomethane (0.004 mol, 0.3 mL). Yield 62%, m.p. = 121–122°C. IR ($\bar{\upsilon}$, cm^{-1}, KBr disk): 3055 (aromatic CH), 2924 (aliphatic CH), 1165 (C-N) st., 1597 aromatic (C=C) st. ^{1}H NMR (400 MHz, d6-DMSO, δ, ppm): 2.5 (s, CH_3, 3H), 3.17 (s, $2CH_3$, 6H), 6.8–7.9 (m, 8H), 2.6–2.9 (m, 3H). ^{13}C-NMR (d6-DMSO, δ, ppm): 20.83 (−$2CH_3$), 21 (aziridine ring), 39.66 (CH), 125.58–148.49 (aromatic carbon).

2-(2,3-Dimethoxyphenyl)-1-tosylaziridine (2b)

It was prepared by reacting N-(2,3-dimethoxybenzylidene)-4-methylbenzenesulfonamide (0.004 mol, 1.2 g) with diiodomethane (0.005 mol, 0.4 mL). Yield 80%, m.p. = 106–108°C. IR ($\bar{\upsilon}$, cm^{-1}, KBr disk): 3047 (aromatic CH), 2916 (aliphatic CH), 1165 (C-N) st., 1535 aromatic (C=C) st.^{1}H-NMR (400 MHz, d6-DMSO, δ, ppm): 2.52 (s, CH_3, 3H), 3.5 (s, $2OCH_3$, 6H), 6.8–7.85 (m, 7H), 2.6–3.3 (m, 3H). ^{13}C-NMR (d6-DMSO, δ, ppm): 60 (−$2OCH_3$), 36 (aziridine-ring), 39.61 (CH), 124.45–154.92 (aromatic carbon).

3-(1-Tosylaziridin-2-yl)indolin-2-one (2c)

It was prepared by reacting 4-methyl-N-(2-oxoindolin-3-ylidene)benzenesulfonamide (0.002 mol, 1.2 g) with diiodomethane (0.002 mol, 0.4 mL). Yield 64%, m.p. = 89–90°C. IR ($\bar{\upsilon}$, cm^{-1}, KBr disk): 3070 (aromatic CH), 2954 (aliphatic CH), 1157 (C-N) st., 1589 aromatic (C=C) st. ^{1}H-NMR (400 MHz, d6-DMSO, δ, ppm): 2.5 (s, CH_3, 3H), 7.3–8.1 (m, 8H), 2.7–2.8 (m, 3H), 10.8 (s, NH). ^{13}C-NMR (d6-DMSO, δ, ppm): 21 (CH_3), 37 (aziridine ring), 119.62–139.12 (aromatic carbon).

4-(1-Tosylaziridin-2-yl)benzaldehyde (2d)

It was prepared by reacting N-(4-formylbenzylidene)-4-methylbenzenesulfonamide (0.003 mol, 1g) with diiodomethane (0.003 mol, 0.6 mL). Yield 82%, m.p. = 230–232°C. IR ($\bar{\upsilon}$, cm^{-1}, KBr disk). 3050 (aromatic CH), 2924 (aliphatic CH), 1157 (C-N) st., 1597 aromatic (C=C) st. ^{1}H-NMR (400 MHz, d6-DMSO, δ, ppm): 2.47 (s, CH_3, 3H), 7.29–8.34 (m, 8H), 2.61–2.69 (m, 3H), 10.21 (s, H-C=O, 1H). ^{13}C-NMR (d6-DMSO, δ, ppm): 20.88 (-CH_3), 28.98 (aziridine ring), 40.08(CH), 125.58–141.83 (aromatic carbon), 192.04 (carbonyl aldehyde).

Determination of cytotoxicity[16]

Different amounts of solutions of aziridines (0.1, 0.2, 0.3, 0.4, and 0.5) mg/ml were prepared. Serial dilutions of the compounds 2(a, b, c, d) were made in phosphate-buffered saline. A total volume of 0.8 ml for each dilution was placed in an Eppendorf tube. A negative control tube (containing saline only) and a positive control tube (containing tap water) were also included in the analysis. Human erythrocytes were added to each tube to give a final volume of 1 ml. Solutions were incubated at 37°C for 30 min. The tubes were then examined for red blood cell decomposition; the experiment was repeated twice.

RESULTS AND DISCUSSION

Aziridines **2** were prepared by the reaction ofsulfonylimine**1** (Schiff bases) with CH_2I_2 in the presence of MeLi at 0°C [**Scheme 1**]. The complete structures and molecular formulas of the products **2** are shown in **Table 1**. The structures of **2** were thoroughly confirmed spectral and analytical data. The starting sulfonylimines were available by the condensation of sulfonylamine with appropriate aldehyde/ketone compounds according to the literature procedure.

Spectral discussion

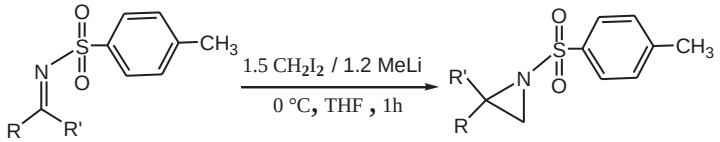
The structures of the aziridines **2a-d** were established on the basis of spectral data, IR, **^{1}H-NMR, ^{13}C-NMR** and satisfactory elemental analyses.

IR spectral IR of 2a

The IR spectrum of N,N-dimethyl-4-(1-tosylaziridin-2-yl)aniline (**2a)** displayed the disappearance of absorption bands corresponding to C=N stretching frequency of imine functional group while the appearance of the absorption band about 1597 cm^{-1}, characteristic of (C-N)cyclic that indicated the formation of aziridine ring functionality in the present of N,N-dimethyl-4-(1-tosylaziridin-2-yl)aniline.

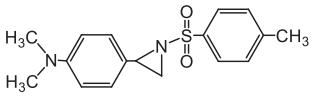
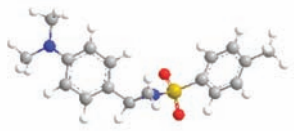
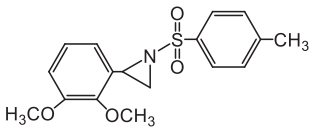
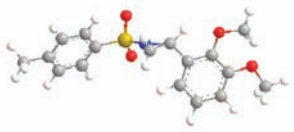
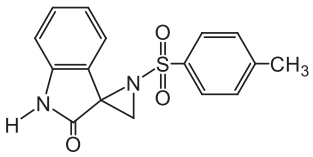
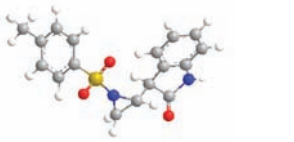
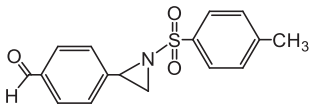
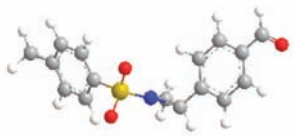
^{1}H-NMR spectral analysis 2a

The ^{1}H NMR spectrum of the newly formed compound showed one singlet at δ = 2.51 ppm for the CH_3 protons and another singlet at δ = 3.2 ppm for the $2CH_3$ protons. The protons of the aziridine ring displayed two signals at δ = 3.02 and 3.37 ppm as singlet, which attributed to CH_2 and CH, respectively. The doublet of doublet signal appeared in the region of δ = 6.90–7.94 ppm integrating for 8 protons confirmed the other aromatic protons.[17]



Scheme 1: General reaction for the synthesis of sulfonylaziridines

Table 1: The chemical structure of prepared aziridine derivatives (2a-d)

No.	Product	Molecular formula MW	Structure formula	Structure three dimension
1	**2a**	$C_{17}H_{20}N_2O_2S$ 316.42		
2	**2b**	$C_{17}H_{19}NO_4S$ 333.40		
3	**2c**	$C_{17}H_{16}N_2O_3S$ 328.39		
4	**2d**	$C_{16}H_{15}NO_3S$ 301.36		

^{13}C-NMR spectral analysis of 2a

The **^{13}C-NMR** spectrum fully supported the proposed structure due to the appearance of signal around **δ** = 20.88 ppm assignable to methyl group, and two carbons of aziridine ring showed two chemical shifts at **δ** = 21 and 39.46 ppm, which confirmed the presence of carbons at **2** and **3-** positions, respectively. The aromatic carbons in the structure of the desired compound were observed at **δ** 125.58–154.94 ppm.[18]

Spectral data of 2-(2,3-dimethoxyphenyl)-1-tosylaziridine (2b)

^{1}H-NMR spectral analysis of 2-(2,3-dimethoxyphenyl)-1-tosylaziridine 2b

^{1}H-NMR spectrum of **2b** showed the following expected signals: Singlet at δ = 2.49 ppm for the CH_3 protons, and singlet at δ =3.40 ppm for the $2OCH_3$ protons. The protons of aziridine ring displayed two signals at δ =2.7 and 3.18 ppm as singlet, which attributed to CH_2 and CH, respectively. The doublet of doublet signal appeared in the region of δ = 6.8–7.84 ppm integrating for 7 protons.

^{13}C-NMR spectral analysis of 2b

The **^{13}C-NMR** spectrum fully supported the proposed structure due to the appearance of the following signals: **δ** 20.89 (methyl), two chemicals 21 and 39.61 (aziridine carbons at **2** and **3**-positions, respectively), (methoxy group), and 124.45–154.92 (aromatic ring carbons).

^{1}H-NMR spectral analysis of 2c

^{1}H-NMR spectrum of **2c** showed the following expected signals – singlet at δ = 2.49 ppm for the CH_3 protons. The protons of the aziridine ring displayed two signals at δ = (2.79–3.02) as singlet, which attributed to CH_2. The doublet of doublet signal appeared in the region of δ =7.26–8.21, integrating for 8 protons and one singlet appeared at δ = 8.82 for –NH of the indole ring.

^{13}C-NMR spectral analysis of 2c

The **^{13}C-NMR** spectrum fully supported the proposed structure due to the appearance of expected signals. Besides the signals due to carbons of methyl group, aziridine ring, and aromatic ring, a signal at **δ** 169.02 appeared due to carbonyl amide of the indolinone ring.

^{1}H-NMR spectral analysis of 2d

^{1}H-NMR spectrum of **2d** showed the following expected signals – one singlet at 2.47 for the CH_3 protons. The protons of the aziridine ring displayed two signals at δ 2.61 and 3.58 as singlet, which attributed to CH_2 and CH, respectively. The doublet of doublet signal appeared in the region of δ =7.46–8.17 ppm, integrating for 8 protons and a singlet at δ 10.24 ppm for aldehydic proton.

^{13}C-NMR spectral analysis of 2d

The **^{13}C-NMR** spectrum fully supported the proposed structure due to the appearance of following signals at **δ** 20.88 (methyl group), 28.98 and 40.08 (carbons of aziridine ring at **2** and **3**-positions), 125.57–141.8 (aromatic ring carbons), and 192.92 (carbonyl aldehyde group).

Cytotoxicity testing

The results of cytotoxicity of the prepared compounds (**2a – d**) in the direction of human red blood cells showed that the compounds 2(a-d) do not carry any toxicity at the concentrations (0.1, 0.2, 0.3, 0.4, and 0.5) mg/ml. Red blood cells have been used to detect the toxicity of prepared compounds because this method is inexpensive, easy to apply, and quick results. This test is the first step to

determine whether to continue or stop working. Red blood cell decomposition depends on the concentration of the material, incubation period, and temperature. The red blood cell crash is due to the breakdown of the red cell membrane due to the cotoxicity between the toxic substances and groups (1) found in the initial structure of the proteins.

CONCLUSION

In this study, four N-sulfonyl aziridines have been synthesized using MeLi as a catalyst compared with the assistant factor; this method gave an excellent result with high yield and the duration of the reaction was shorter.

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