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Synthesis of Morpholine Containing Sulfonamides: Introduction of Morpholine Moiety on Amine Functional Group

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Abstract Sulfonamides have been the center of drug structures as this group is quite stable & well tolerated in human beings. The synthesis of these structures was started in search of new pharmacological active reagents. These compounds are being tested for the desired activity (ICAM-1/LFA-1 Interaction inhibitors as anti-adhesion therapeutic agents), the biological activity & structure activity relationship will be published elsewhere. Synthesis of morpholine moiety from amino group is done by using reagent 2-chloroethanol.

Key words: Sulfonamides, Morpholine, anti-adhesion molecules.

Introduction

Sulfonamides have been the center of drug structures as this group is quite stable & well tolerated in human beings. The synthesis of these structures was started in search of new pharmacological active reagents. These compounds are being tested for the desired activity (ICAM-1/LFA-1 Interaction inhibitors as anti-adhesion therapeutic agents¹), the biological activity & structure activity relationship will be published elsewhere.

Synthesis of sulfonamide² based target compounds involved coupling reactions under different conditions and reduction of the nitro compounds. Elucidation of the structures is done on the basis of ¹H NMR, FTIR & confirmed with MS analysis.

Synthetic Schemes

The synthetic scheme employed involves a key intermediate sulfonamide GD₂ are summarized as follows.

Scheme 1

Scheme 1 depicts the synthesis of GD_1 (Sulfonamide). Sulfonamide synthesis involve the reaction of sulphonyl chloride with amines either in acetone or in basic aqueous media.³ Feebly basic amines, e.g. the nitroanilines, generally react so slow with benzene sulfonyl chloride that most of the acid chloride is hydrolyzed by the aqueous alkali before a reasonable yield of the sulfonamide is produced; indeed, *o*-nitroaniline gives little or no sulfonamide under normal reaction conditions.³ When reaction was carried out in pyridine, the yields were high. The reaction was observed to be time dependent. More than 30 min. resulted a di-sulfonyl substituted nitroaniline with similar R_f value in TLC, but being insoluble in rectified spirit. This formed the basis of purification by differential solubility.

Reduction of nitro group in GD_1 is done by using Zn/NaOH reduction method.³ This method was preferred over tin/HCl or stannous chloride in acid because of better yield and is less time consuming. TLC plate showed four spots, which gave three spots in diethyl ether solution (impurities). Hence, diethyl ether washing was selected to purify the product. Amount of zinc was increased more than normal to reduce the impurities and time of reaction. This reaction was used in all other reductions and worked well with high yields. The only precaution to be observed is that the ratio of NaOH & rectified spirit should be kept constant irrespective of the starting compound taken.

Scheme 2

Scheme 2 indicate the formation of GD_3 , a simple coupling involving loss of HCl and the reaction was completed with refluxing in N,N-dimethyl formamide for 16 Hr. DMF is chosen as a high boiling organic solvent, miscible with water. On pouring this solution in ice water GD_3 precipitated out.

Following this GD_3 is reduced to GD_4 using standardized Zn/NaOH reduction procedure as for GD_2 . Following this was coupling of GD_4 with 2-chloroethanol⁴ to form GD_5 . Amine is replaced by morpholine functionality. Amine can be diazotised and then morpholine can replace the diazo group. The reaction with 2-chloroethanol was designed using the fact that alkyl chloride couple with aromatic amines at temperature 58°C with stirring in dioxane in 40 Hr. The time was kept same but conditions made more severe involving more potassium carbonate and refluxing conditions. The reactant spot (GD_4) on TLC disappeared from reaction mixture after 11 Hrs. As we were not sure of cyclization, the reaction was continued for 40 Hrs. The worked up reaction showed no intermediate product. Reduction of reaction time was not attempted.

Scheme 3

Scheme 3 depicts the synthesis of GD_9 . *Ortho*-Chloro nitrobenzene being more crowded requires severe conditions to couple with GD_2 . Addition of potassium carbonate and increase in time to 24 Hrs served the purpose.³ The reaction followed a peculiar pattern in that if severe refluxing was done, the product isolated was containing an oily material (yellow in color). Oil mixed with product and was not separable with solubility technique. It could only be separated by heating, as the liquid evaporated easily and leaving solid product behind, but care was taken not to char product and avoid constant heating to stop bumping of the whole product. Whole problem was avoided with controlled refluxing conditions. Other reactions were same as in **scheme 2**.

Scheme 4

Scheme 4 indicates formation of **GD₁₃**. The formation of **GD_{2A}**, from 4-nitro toluene was done by bromination, using standard N-Bromo succinimide.³ Dibenzoyl peroxide was used as free radical chain initiator in CCl_4 , forming a pure product. **GD_{2A}** being alkyl halide also need severe conditions like in **scheme 3**. Other reactions were same as in **scheme 3**.

Obervation Data

Synthesised compounds were purified and their structure was elucidated based on $^1\text{H-NMR}$ (Table 3) & IR data (Table 2). The structures were further confirmed by Mass Spectra (data not shown)

Name/Compd. No.	Sol. in Water	Recrys. Solvent	Melting Point °C	% yield
N-(2-nitrophenyl) benzene sulfonamide (GD ₁)	-	C ₂ H ₅ OH	107-108	89.94
N-(2-aminophenyl) benzene sulphonamide (GD ₂)	+	CH ₃ OH	121-122	96.52
N-{2-[(4-nitrophenyl) amino] phenyl}benzenesulfonamide (GD ₃)	-	CH ₃ OH	162-163	54.2
N-{2-[(4-aminophenyl) amino] phenyl} benzenesulfonamide (GD ₄)	+	CHCl ₃	184-185	89.2
N-{2-[4-(4-morpholino)anilino] phenyl} benzenesulfonamide (GD ₅)	-	CH ₃ OH	209-210	88.71
1-(bromomethyl)-4-nitrobenzene(GD _{2A})	-	C ₂ H ₅ OH	100-101	81.4
N-{2-[(2-nitrophenyl) amino] phenyl}benzenesulfonamide (GD ₇)	-	CH ₃ OH	148-149	53.09
N-{2-[(2-aminophenyl) amino] phenyl} benzenesulfonamide (GD ₈)	+	CHCl ₃	168-169	88.7
N-{2-[2-(4-morpholino) anilino] phenyl} benzenesulfonamide (GD ₉)	-	CH ₃ OH	194-195	79.2
N-{2-[(4-nitrobenzyl) amino] phenyl}benzenesulfonamide (GD ₁₁)	-	CH ₃ OH	179-180	50.12
N-{2-[(2aminobenzyl) amino] phenyl}benzenesulphonamide (GD ₁₂)	+	CHCl ₃	197-198	90
N-{2-[4-(4-morpholino) benzylamino] phenyl} benzenesulfonamide (GD ₁₃)	-	CH ₃ OH	219-220	83.45

Table 2 IR Data (KBr Pellets)

Comp. GD _N /N→	1	2	3	4	5	2A	7	8	9	11	12	13
IR Frequency present												
N-H str. (sulphonamide)	+	+	+	+	+	-	+	+	+	+	+	+
Asym./Sym. N-H str. (Amine)	-	+	+	+	+	-	+	+	+	+	+	+
Ar C-H str. (asym/Sym)	+	+	+	+	+	+	+	+	+	+	+	+
Asym./Sym. N(=O) ₂ str.	+	-	+	-	-	+	+	-	-	+	-	-
Asym./Sym.S(=O) ₂ stretching	+	+	+	+	+	-	+	+	+	+	+	+
Asym/SymC-O-C str.	-	-	-	-	+	-	-	-	+	-	-	+

Table 3 NMR DATA (CDCl₃)

Compd. No.; δ (ppm); No. of protons; Multiplicity; J (hertz)
GD ₁ ⇒ δ 9.86:1H, s; δ 8.11:1H, dd (J=8.2; 1.3); δ 7.97:1H, d (J=7.9); δ 7.85:2H, d (J=7.8); δ 7.58:2H, m; δ 7.47:1H, t (J=7.6); δ 7.26:1H, s; δ 7.16:1H, t (J=7.9).
GD ₂ ⇒ δ 7.77:1H, t (J=7.3); δ 7.51:2H, d (J=7.2); δ 7.27:3H, t (J=7.1); δ 7.06:1H, t (J=6.7); δ 6.75:1H, d (J=7.99); δ 6.49:1H, m; δ 4.08:1H, s (broad); δ 1.62:2H, s (broad).
GD ₃ ⇒ d 8.22:7H, dd (J=7.1; ≈2); d 7.55:7H, dd (J=7.1; ≈2); d 7.29:1H, s
GD ₄ ⇒ d 8.29:1H, s; d 7.95:6H, d (J=8.7); d 7.67:6H, d (J=8.7); d 7.40:1H, d (J=8.7); d 6.93:1H, d (J=8.7); d 3.39:2H, s (broad)
GD ₅ ⇒ d 7.9:1H, d (J=2); d 7.8:1H, d (J=2); d 7.73:1H, dd (J=6.9; 1.3); d 7.51:5H, m; d 7.33:2H, d (J=10.85); d 7.15:2H, d (J=9.725); d 6.75:3H, m; d 4.53:4H, m; d 3.76:4H, m.
GD _{2A} ⇒ d 8.20:2H, d (J=8.6); d 7.59:2H, d (J=8.6); d 4.55:2H, s.
GD ₇ ⇒ d 7.76:3H, d (J=7); d 7.53:4H, m; d 7.27:1H, s; d 7.05:1H, t (J=7); d 6.74:1H, d (J=7); d 6.49:3H, m; d 3.71:2H, s (broad).
GD ₈ ⇒ d 8.28:1H, d (J=8); d 7.73:4H, m; d 7.34:5H, m; d 6.82:1H, m; d 6.37:3H, t (J=8); d 6.20:1H, d (J=6); d 3.58:2H, s (broad).
GD ₉ ⇒ d 7.915:1H, d (J=6); d 7.698:2H, m; d 7.48:5H, m; d 7.20915:2H, s; d 7.1978:1H, t (J=11.72); d 6.8125:1H, dd (J=7.7; 1.3); d 6.65:1H, m; d 6.43:1H, m; d 6.18:1H, m; d 4.1378:1H, m; d 3.6466:2H, m; d 3.363:2H, m; d 3.06:1H, m; d 2.8602:1H, m; d 1.1941:1H, s
GD ₁₁ ⇒ d 8.09625:2H, d (J=8.1); d 7.815475:2H, d (J=8.05); d 7.6278:3H, m; d 7.39855:3H, m; d 7.21415:4H, m; d 6.8865:1H, m; d 4.31:1H, d (J=15.31); d 3.9366:1H, d (J=15.36).
GD ₁₂ ⇒ d 8.535:3H, s; d 8.3:2H, s; d 7.64:4H, m; d 7.125:3H, m; d 6.65:2H, m; d 3.8:3H, m; d 2.5675:1H, d (J=18.75); d 1.13:1H, d (J=17.29).
GD ₁₃ ⇒ d 7.84:5H, m; d 7.27:8H, m; d 6.74:2H, m; d 4.01:1H, m; d 3.75:1H, m; d 3.60:1H, d (J=12); d 3.20:1H, d (J=12); d 2.45:1H, m; d 2.25:1H, m; d 1.75:2H, m; d 1.50:1H, m; d 1.25:2H, m.

Results and Discussion

The morpholine based sulfonamides were successfully synthesized and their structure well elucidated. These compounds are being tested for the desired activity in our pharmacology division in the department.

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