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Synthesis of 4-Alkoxy-3-Methasulfonamido Acetophenone based potential cyclooxygenase-2-Inhibitors

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Abstract

The present work was designed to synthesis novel methane sulfonamido substituted alkyl aryl ethers and establishment of authenticity and purity of the prepared compounds utilizing various spectral and chromatographic techniques. Methods: The synthetic scheme followed for the preparation of the compound AB1 and AB2 followed 2-aminophenol was subjected to Friedel craft's acylation reaction. The next step in the synthesis scheme involved generation of ether linkage at the phenolic –OH position in AB2, resulting in final compound AB3 to AB7.The alkyl bromide which was reacted with AB2 in the presence of basic solvent pyridine giving satisfactory yield of the ether product, due to insolubility of AB2 in triethylamine. Results and conclusion: IR, Mass and NMR have confirmed the synthesis of the compounds from AB1 to AB8. Purification of the compounds was done by TLC. Hence, present study exhibited that novel methane sulfonamido substituted alkyl aryl ethers may be used as synthetic compounds for anti-inflammatory activity with minimum side effects.

Key words: Antinflammatory, methane sulfonamido, analgesic, Friedel craft's

I INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) represent a class of drugs widely used for treatment of symptoms of acute and chronic inflammatory disorders such as osteoarthritis and rheumatoid arthritis. Selective COX-2 inhibitors have the same anti-inflammatory, antipyretic, and analgesic activities as traditional NSAIDs and are safer with respect to gastrointestinal tract side effects [1]. However COX-2 also exists and has physiological functions in various normal tissues such as kidney, pancrease, brain and female genital organs. Ever since the discovery of the COX-2 isoform of cyclo-oxygenase enzyme and its implication in inflammatory conditions, studies are being extensively pursued for the development of agents

with selective COX-2/COX-1 affinity. Drug development work in this area has led to the identification of two distinct chemical classes and most of the current research in the area is basically along designing of representative compounds [2]. The diaryl substituted heterocycles is extensively studied class and several heterocyclic and carboxylic variations of the central ring have been explored. The methane sulfonyl/sulphonamide substituted aryl ethers/ thioethers represents the second chemical class with highly successful example of nimesulide [3]. All the compounds currently reported in literature possess one common structural feature i.e. the presence of CH_3SO_2-(methylsulfonyl) or CH_3SO_2 NH-(methanesulfonamido) moieties on the aromatic systems. Most of the SAR studies have also been carried out the modifications in rest of the molecule, while retaining this structural feature, accepting it as a prerequisite for activity. The relatively unexplored second chemical class of aryl ether can be taken as a basic for further research. The present work was designed to synthesis novel methane sulfonamido substituted alkyl aryl ethers and establishment of authenticity and purity of the prepared compounds utilising spectral and chromatographic techniques.

II EXPRIMENTAL WORK

A. *Synthesis of 3-amino-4-hydroxy acetophenone (AB_1)*

A homogeneous solution of 4g (36.6m) of 2-aminophenol and 20 ml of nitrobenzene was taken and to this solution 2.4ml (33.8 Mm) of acetyl chloride was added. Further 4.592 g (34.8 mM) of aluminium chloride was added in small portion during 90 min. The reaction mixture was poured into chilled water and filtered. Filtrate was washed with diethyl ether. Aqueous layer was evaporated in vacuo yielding the crude product as dark coloured solid. The total yield was 59% and melting point was74 ^{0}C.

B. *Synthesis of 4-hydroxy-3-methanesulfonamido acetophenone (AB_2)*

Briefly, 1g (6.6 mM) of crude acetyl-2-amino phenol was stirred with 60 ml of dichloromethane and filtered. To this mixture, triethylamine 6 ml (43.1mM) and methanesulfonylchloride (6ml, 7.7 mM) were added. Reaction mixture was stirred at room temperature for 13 h. The solvent was evaporated to give the final product, recrystallization from toluene yielded the final product as light brown crystals. The total yield was 54% and melting point was 118 ºC.

C. *Synthesis of 4-ethoxy-3-methanesulfonamido acetophenone (AB_3)*

In brief, 2g (8.7mM) of 4-hydroxy 3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine. To the resulting solution, 2 ml (24.7 mM) of 1-bromoethane and refluxation was carried out at 50 ºC for 20 h. Reaction mixture was cooled and partitioned between 1 M sodium hydroxide and diethyl ether. The organic layer was washed with thrice with 20 ml of 1 M HCl. Solvent was removed in vacuo affording the product as solid. The total yield was 63% and melting point was 72 ºC.

D. *Synthesis of 4-propoxy-3-methanesulfonamido acetophenone (AB_4)*

Briefly, 2g (8.7 mM) of 4-hydroxy 3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine. Resulting solution was added to 2 ml (21.8 mM) of 1-bromopropane and refluxation was carried out at 50ºC for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml brine. Solvent was removed in vacuo affording the product as solid. The total yield was 54% and melting point was 78 ºC.

E. *Synthesis of 4-butoxy-3-methanesulfonamido acetophenone (AB_5)*

In brief, 2g (8.7 mM) of hydroxyl 3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine. To the resulting solution, 2 ml (18.5 mM) of 1-bromobutane and refluxation was carried out at 50 ºC for 20 h. Reaction mixture was cooled and partitioned between 1 M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1 M HCl followed by washing with 20 ml brine, and dried using anhydrous sodium sulphate. Solvent was removed in vacuo affording the product as solid. The total yield was 54% and melting point was 85 ºC.

F. *Synthesis of 4-pentoxy-3-methanesulfonamido acetophenone (AB_6)*

Synthesis was carried out by weighing 2g (8.7mM) of 4-hydroxy 3-methanesulfonamido acetophenone and dissolved in 7.0 ml of pyridine. To the resulting solution, 2 ml (16.0 mM) of 1-bromopentane and refluxation was carried out at 50ºC for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml brine, and dried using anhydrous sodium sulphate. The total yield was 54% and melting point was 90 ºC.

G. *Synthesis of 4-hexoxy-3-methanesulfonamido acetophenone (AB_7)*

In brief, 2g (8.7 mM) of 4-hydroxy 3-methasulfonamido acetophenone was dissolved in 7.0 ml of pyridine. To the resulting solution, 2 ml (14.2 mM) of 1-bromohexane and refluxing was carried out at 50ºC for 20 h. Reaction mixture was cooled and partitioned between 1 M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1 M HCl followed by washing with 20 ml brine, and dried using anhydrous sodium sulphate. Solvent was removed. The total yield was 52% and melting point was 92 ºC.

H. Synthesis of 4-ethoxy-3-ethylamine acetophenone (AB_8)

Briefly, 2g (8.7mM) of 4-hydroxy-3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine and 0.82g (14.6 mM) of potassium hydroxide was suspended into this solution. To the resulting viscous solution, 2 ml (24.7mm) of 1-bromoethane was added and refluxation was carried out for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml brine, and dried using anhydrous sodium sulfate. Solvent was removed. The total yield was 66% and melting point was 87 ºC.

I. Synthesis of 4-propoxy-3-propylamino acetophenone (AB_9)

Briefly, 2g (8.7 mM) of 4-hydroxy 3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine and 0.82 g (14.6 mM) of potassium hydroxide was dissolved in 7.0 ml of pyridine and 0.82 g (14.6mm) of potassium hydroxide was suspended into this solution. To the resulting viscous solution, 2 ml (21.8 mM) of 1-bromopropane and refluxation was carried out for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml brine. The total yield was 63% and melting point was 90 ºC.

J. Synthesis of 4-butoxy-3-butylamino acetophenone (AB_{10})

Briefly 2g (8.7mm) of 4-hydroxy 3-methanesulfonamidoacetophenone was dissolved in 7.0 ml of pyridine and 0.82 g (14.6 mM) of potassium hydroxide was suspended into this solution. To the resulting viscous solution, 2 ml (18.5 mM) of 1-bromobutane was added and refluxation was carried out for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethylether. The organic layer was washed thrice with 20 ml of 1 M HCl and dried using anhydrous sulfate. The total yield was 62% and melting point was 90 ºC.

K. Synthesis of 4-pentoxy-3-pentylamino acetophnone (AB_{11})

Briefly 2g (8.7mm) of 4-hydroxy-3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine and 0.82g (14.6 mM) of potassium hydroxide was suspended into this solution. To the resulting solution 2 ml (16.0 mM) of 1-bromopentane and refluxation was carried out for 20 h. Reaction mixture was cooled and partitioned between 1 M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml brine, and dried using anhydrous sodium sulphate The total yield was 55% and melting point was 92 ºC.

L. Synthesis of 4-hexoxy-3-hexylamino acetophenone (AB_{12})

In brief, 2g (8.7 mM) of 4-hydroxy 3-methanesulfonamido acetophenone was dissolved in 7.0 ml of pyridine and 0.82g (14.6 mM) of potassium hydroxide was suspended into this solution. To the resulting viscous solution, 2 ml (14.2 mM) of 1-bromohexane and refluxation was carried out for 20 h. Reaction mixture was cooled and partitioned between 1M sodium hydroxide and diethyl ether. The organic layer was washed thrice with 20 ml of 1M HCl followed by washing with 20 ml of brine, and dried using anhydrous sodium

sulfate. Solvent was removed. The total yield was 51% and melting point was 92 ºC.

III RESULTS AND DISCUSSION

A. Synthetic scheme for AB_1 and AB_2

The synthetic scheme followed for the preparation of the compound AB1 and AB2 using 2-aminophenol was subjected to Friedel craft's acylation reaction. 2-aminophenol was not soluble in common organic solvents such as toluene. Hence nitrobenzene was employed as solvent in this reaction. The resulting product was purified by pouring over ice water followed by ether extraction in the initial trial. Procedure for removing nitrobenzene through steam distillation was unsuccessful as it led to the decomposition of final product [5]. 2-amino phenol reaction was carried out with acetyl chloride in presence of aluminium chloride at 0ºC.The mechanism of this reaction is postulated to involve an acylium ion as the electrophilic species although an electrophillic complex between the acid chloride and almunium chloride may also be involved. The same reaction was also successful when carried out in pyridine; however the reaction monitoring was difficult in the later case as pyridine spot obscured the chromatogram.

B. Scheme 2

The next step in the synthesis scheme involved generation of ether linkage at the phenolic-OH position in AB2, resulting in final compound AB3 to AB7. The alkyl bromide which was reacted with AB2 in the presence of basic solvent pyridine giving satisfactory yield of the ether product, due to insolubility of AB2 in triethylamine, later could not be employed as a solvent in this case. However in this case, the sulphonamide linkage got hydrolyzed to the corresponding primary aromatic amine which in turn underwent nucleophilic substitution reaction with the alkyl halide being taken for etherification resulting in distributed compounds AB8, AB9, AB10, AB11 and AB12. This scheme protected the sulfonamido grouping with the appropriate alkyl halides.

C. Characterization of AB8 to AB12 using IR, NMR and Mass spectroscopy

The synthesized compounds were characterized using IR (Table 1-5), NMR and mass spectroscopy (data not shown).

Table 1: FTIR assignment of 4-Ethoxy-ethylamine acetophenone (AB_8)

FTIR peaks	Assignments
3500-3050cm^{-1}	v, Broad N-H stretch
3150cm^{-1}	v, aromatic C-H strech
2900,2850cm^{-1}	v, aliphatic C-H strech
1640cm^{-1}	v, aromatic C=O strech
1460cm^{-1}	v, C-C ring strech
1380cm^{-1}	v, C-H bend
1250cm^{-1}	v, Asymmetric C-O-C stretch
1020cm^{-1}	Symmetric C-O-C stretch
1000m^{-1}	in plane C-H bends

Table 2: FTIR assignment of 4-Propoxy-propylamino acetophenone (AB_9)

FTIR peaks	Assignments
3500-3100cm^{-1}	v, Broad N-H stretch
3100cm^{-1}	v, aromatic C-H strech
2910,2850cm^{-1}	v, aliphatic C-H strech
1640cm^{-1}	v, aromatic C=O strech
1600cm^{-1}	v, C-C ring strech
1460,1385cm^{-1}	v, C-H bend
1220cm^{-1}	v, AsymmetricC-O-C strech
1200cm^{-1}	C-N stretch
1100 ,1000m^{-1}	in plane C-H bend
1020cm^{-1}	symmetric C-O-C strectch
700cm^{-1}	out of plane ring C=C bend ring

Table 3: FTIR assignment of 4-butoxy-butylamino acetophenone (AB_{10})

FTIR peaks	Assignments
3500-3100cm^{-1}	v, Broad N-H stretch
3100,3000cm^{-1}	v, aromatic C-H strech
2930,2850cm^{-1}	v, aliphatic C-H strech
1640cm^{-1}	v, aromatic C=O strech
1600,1460cm^{-1}	v, C-C ring strech
1460,1385cm^{-1}	v, C-H bend
1220cm^{-1}	v, AsymmetricC-O-C strech
1385cm^{-1}	C-N stretch
1200cm^{-1}	in plane C-H bend
1010cm^{-1}	symmetric C-O-C strectch
710cm^{-1}	out of plane ring C=C bend ring

Table 4: FTIR assignment of 4-Pentoxy-pentylamino acetophenone (AB_{11})

FTIR peaks	Assignments
3500-3100cm^{-1}	v, Broad N-H stretch
3100cm^{-1}	v, aromatic C-H strech
2900,2825cm^{-1}	v, aliphatic C-H strech
1630cm^{-1}	v, aromatic C=O strech
1450cm^{-1}	v, C-C ring strech
1385cm^{-1}	v, C-H bend
1000cm^{-1}	v, C-O stretch
700cm^{-1}	out of plane ring C=C bend

Table 5: FTIR assignment of 4-Hexoxy-hexylamino acetophenone (AB_{12})

FTIR peaks	Assignments
3500-3100cm^{-1}	v, Broad N-H stretch
3050cm^{-1}	v, aromatic C-H strech
2920,2800cm^{-1}	v, aliphatic C-H strech
1660cm^{-1}	v, aromatic C=O strech
1600,1460cm^{-1}	v, C-C ring strech
1385cm^{-1}	v, C-H bend
1210cm^{-1}	v, Asymmetric C-O-C stretch
1195cm^{-1}	C-N stretch
1120m^{-1}	symmetric C-O-C stretch
1020cm^{-1}	in plane C-H bend
750cm^{-1}	C-H bend

IV DISCUSSION AND CONCLUSION

The current research work was undertaken to design and synthesize novel compounds with potential to act as selective COX-2 (vs COX-1) inhibitors. Such agents would block prostaglandins production at the site of inflammation without affecting beneficial prostaglandins in normal tissues such as stomach and kidney. Thus demonstrating an anti inflammatory action devoid of gastrointestinal and renal toxicity [6]. Diaryl substituted heterocycles have been extensively studied in this regard. This class incorporates a central heterocyclic ring (e.g, thiophene, pyrazole, pyrole and imidazole) substituted by two aryl moieties mostly in a 1-2 arrangement, as initial reports relate

to compounds containing methylsulfone and sulfomyl moieties attached to one of the aromatic systems. Several reports suggest that this grouping is essential for COX-2/COX-1 selectivity. Further carboxylic isosteric replacement for the central heterocyle have also culminated in the discovery of important COX-2 selective inhibitors which suggests that the central ring is important for leading a particular orientation to the two aryl systems. Additionally, it may also contribute towards the receptors binding through Vander Waals interactions with a complementary lipophilic region. The second major class of selective COX-2 inhibitors is of methyl sulfonyl/sulfonamido aryl ethers/thioethers which was exploited for selecting a template for the design strategy. The active compound of the series NS-398, nimeuslide and CGP-28238 (flosulide) contain a nitro substituted aryl ether moiety and an indanone aryl ether moiety comparable conditions [7]. The presence of methyl sulfone and methyl sulfonamide moiety is another common structural feature in most of the selective COX-2 inhibitors. The present series of compounds have been designed taking into consideration the pharmacophoric requirements as evident from existing compound.

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