Synthesis of Some Sulfonamide Chalcones of Biological Interest

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Abstract

Sulfonamide compounds, identified as chemotherapeutic agents, possess broad spectrum of biological properties. Benzenesulfonamides substituted on N of sulfonamido group such as, sulfathiazole, sulfapyridine, sulfadiazine etc are known to possess broad spectrum of biological properties. This work reported the synthesis of series of N-[4-cinnamoylphenyl]-4-methylsulfonamide by Claisen-Schmidt condensation of N-(4-acetylphenyl)-4-methylbenzenesulfonamide with aromatic aldehydes in presence of 40% NaOH in ethanol at room temperature with higher yields

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Keywords: Tolyl sulfonamides, chalcones, Claisen-Schmidt condensation

Introduction

Chalcones, 1,3-diphenylpropenones are precursor of flavonoids and isoflavonoids, abundantly present in edible plants like vegeTables, fruits, tea and soy, and are essential secondary metabolites in many plants and in bacteria. Since, easy availability of this potent tool naturally as well as synthetically, biological studies has been done by many research groups to display potent array of pharmacological activities such as anti-protozoal, anti-inflammatory, immuno-modulatory, nitric oxide inhibitory, anticancer, anticancer effects and anti-HIV activities.

Sulfonamide compounds, identified as chemotherapeutic agents, possess broad spectrum of biological properties. Benzenesulfonamides substituted on N of sulfonamido group such as, sulphathiazole, sulphapyridine, sulphadiazine etc is known to possess broad spectrum of biological properties Sulphonamides with various heterocyclic rings like pyrazole, isoxazole, furanone ring constitute the present day anti-inflammatory drug such as Rofecoxib, Celecoxib and Valdecoxib. Recently, **Introduction** of sulfonamide group into chalcone scaffold also proves potent tool for the designing of even more potent biological value such as α-glucosidase inhibitors, selective TcTS inhibitors.

Chalcones are usually synthesized from acetophenones and benzaldehydes via the Claisen-Schmidt condensation, using base in a polar solvent. The use of several other catalysts such as KOH, basic alumina, zinc chloride, Lewis acid such as BF_3, $AlCl_3$, Mg-Al-OBu hydrotalcite, has also been reported. Other reagents and conditions have also been used, including the use of strong alkali catalysts under phase transfer conditions, barium hydroxide in ethanol, calcine $NaNO_3$/natural phosphate, potassium phosphate, the use of M.W. conditions, and ultrasonic conditions. Withers et al reported synthesis of

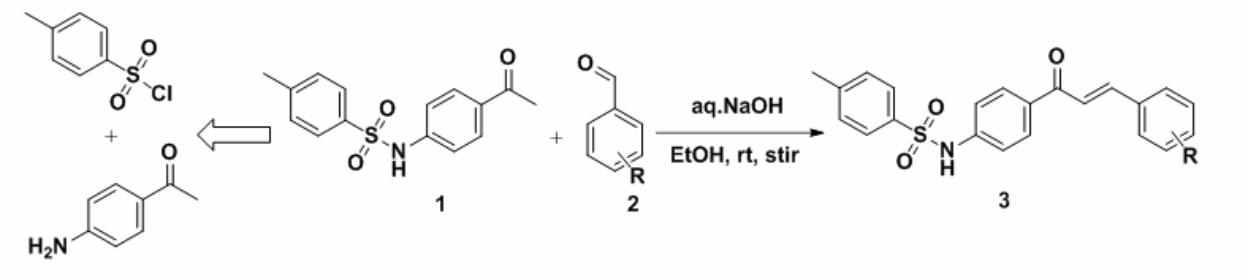
hydroxyl derivatives of sulfonamide Chalcones utizing H_2SO_4 in Methanol under reflux conditions. However harsh reaction conditions with conventional heating needs further improvement in the synthetic strategies.

So, here we report the simple, effective protocol for the synthesis of sulfonamide Chalcones using 40% NaOH in Ethanol at room temperature, depriving the use of harsh reaction conditions altogether with conventional heating procedures.

Results and Discussions

To include the sulfonamide moiety in the destined motif, we prepared starting ketone by condensation of 4-aminoacetophenone and toulenesulfonic chloride in the presence of pyridine.

Later on by utilizing different aromatic aldehydes with this starting ketone, we accessed a series of substituted chalcone (3a-3n) with better yields (Scheme 1).



Scheme 1: Synthetic strategy of Substituted Chalcones

By utilizing optimized reaction conditions, we further improves the scope of this protocol by synthesizing the series of tolyl sulfonamide chalcone derivcatives (Table 1).

Synthesized compounds were characterized by combined application of IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The IR spectra of the compounds showed sharp band around 1650 cm^{-1} respectively due to C - O stretch whereas two peaks observed around 1330 & 1160 cm^{-1} observed for symmetric & asymmetric stretching of SO_2 group ^{1}H NMR spectra of the compounds revealed the presence of singlet at δ 2.32 of tolyl methyl protons. Another singlet for NH proton much downfield around δ 10 is also observed, while CH=CH protons deshielded with aromatic protons in the range of δ 7-8. Mass spectra of the compounds showed molecular ion peak at their respective values.

Experimental

All solvents and chemicals were obtained commercially and were used as received. Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded using a Spectrum-60 spectrometer instrument. NMR spectra were taken with a Bruker Avance II at 400 MHz / Bruker DMX spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as internal standard.

Table 1: Derivatization and Physical Data of Tolyl Sulfonamide Chalcone

Entry	R	Yield[a] (%)	m.p (°C)
3a	Ph	92	150-152
3b	4-OMe	89	155-157
3c	4-Cl	90	181-182
3d	2-Cl	87	184-185
3e	4-F	85	185-187
3f	3-Br	80	228-230
3g	4-Br	85	190-191
3h	4-NMe_2	74	165-166
3i	4-NO_2	85	240-242
3j	4-$CH(CH_3)_3$	94	105-106
3k	4-Me	89	209-210
3k	3-Cl	87	187-188
3l	2-Br	80	208-210
3m	2-furyl	75	138-140
3n	3,4,5-OMe	81	195-196

Isolated pure yield

General procedure for the synthesis of N-(4-acetylphenyl)-4-methylbenzenesulfonamide (1)

To a solution of 4-aminoacetophenone (0.025 mol) and Toulene Sulfonic chloride (0.025 mol) in ethanol, pyridine (0.025 mol) was added dropwise with constant stirring. The solid cake was obtained after 1 hr of constant stirring at room temperature. Completion of reaction is checked over precoated TLC (30% EtOAc:Hexane). Then it is quenched with excess of acidified water. The solid obtained was filtered, washed with 2% $NaHCO_3$ dried. Crude solid obtained is recrystallised in EtOH:H_2O (1:1) to get pure solid.

General procedure for the synthesis of substituted Chalcones

To a solution of 1(0.025 mol) and aromatic aldehyde (0.025 mol) in ethanol, aqueous NaOH (40%) was added dropwise with constant stirring till solid cake was obtained. Constant stirring continued for 20-30min at room temperature and then the reaction mass kept as it is for overnight. Completion of reaction is checked over precoated TLC (30% EtOAc:Hexane). Then it is quenched with excess of acidified water. The solid obtained was filtered, washed with 2% $NaHCO_3$ dried & recrystallized from ethanol.

Analytical data of some new compounds are given below.

N-(4-acetylphenyl)-4-methylbenzenesulfonamide (1)

Yellow solid; yield 90%, Rf 0.5 (30% EtOAc:Hexane), mp 190-192°C

IR: 3219 (NH), 1649(C=O) cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δppm: 2.32 (s, 3H, $-CH_3Ph$), 2.50 (s, 3H, $-COCH_3$), 7.18-7.83 (m, 8H, Ar-H), 10.81 (s, 1H, -NH).

^{13}C NMR (100MHz, CDCl3): 21.5, 27.0, 116.8, 128.9, 129.2, 129.7, 130.4, 137.0, 137.5, 143.1, 196.9

ESMS (m/z) $[M+Na]^+$: 512.0925 (Calcd. 289.0773)

N-(4-cinnamoylphenyl)-4-methylbenzenesulfonamide (3a)

Pale Yellow solid; yield 92%, Rf 0.6 (30% EtOAc:Hexane), mp 150-152°C

IR: 3219 (NH), 1649(C=O), 1336 & 1163 (SO2 asymm. & unsymm.) cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δppm: 2.43(s, 3H, $-CH_3Ph$), 7.27-8.77 (m, 14H, Ar-H, CH=CH), 10.80 (s, 1H, NH)

^{13}C NMR (100 MHz, CDCl3): 25.8, 115.1, 116.0, 123.3, 126.5, 128.8, 129.6, 131.0, 131.8, 132.1, 138.0, 138.9, 143.4, 149.2, 168.1, 189.7.

ESMS (m/z) $[M+H]^+$: 378.1226 (Calcd. 377.1086).

N-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)-4-methylbenzenesulfonamide (3b)

Yellow solid; yield 89%, Rf 0.56 (30% EtOAc:Hexane), mp 155-157°C

IR: 3180 (NH), 1666 (C=O), 1359 & 1170 (SO2 asymm. & unsymm.) cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δppm: 2.41(s, 3H, $-CH_3Ph$), 7.27-8.9 (m, 14H, Ar-H, CH=CH), 10.91 (s, 1H, NH)

^{13}C NMR (100 MHz, CDCl3): 23.0, 115.9, 117.0, 123.5, 126.4, 129.0, 129.9, 131.3, 131.8, 132.1, 138.0, 139.0, 143.4, 148.2, 169.1, 189.0.

ESMS (m/z) $[M+H]^+$: 408.1300 (Calcd. 407.1191).

N-(4-(3-(4-chlorophenyl)acryloyl)phenyl)-4-methylbenzenesulfonamide (3d)

Pale Yellow solid; yield 87%, Rf 0.58 (30% EtOAc:Hexane), mp 181-182°C

IR: 3113 (NH), 1651 (C=O), 1359 & 1155 (SO2 asymm. & unsymm.) cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δppm: 2.49(s, 3H, $-CH_3Ph$), 7.19-8.70 (m, 14H, Ar-H, CH=CH), 10.78 (s, 1H, NH)

^{13}C NMR (100 MHz, CDCl3) : 21.9, 115.3, 118.3, 122.1, 127.2, 128.1, 129.8, 131.2, 131.6, 132.8, 138.0, 138.7, 143.5, 147.2, 164.0, 190.0.

ESMS (m/z) $[M+H]^+$: 413.390 (Calcd. 411.0696)

N-(4-(3-(4-fluorophenyl)acryloyl)phenyl)-4-methylbenzenesulfonamide (3e)

Pale Yellow solid; yield 85%, Rf 0.61 (30% EtOAc:Hexane), mp 171-172°C

IR: 3155 (NH), 1623 (C=O), 1378 & 1134 (SO2 asymm. & unsymm.) cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δppm: 2.45(s, 3H, -CH_3Ph), 7.2-8.8 (m, 14H, Ar-H, CH=CH), 10.9 (s, 1H, NH)

^{13}C NMR (100 MHz, CDCl3): 22.2, 115.5, 117.1, 122.5, 127.0, 128.1, 129.0, 131.0, 131.3, 132.4, 137.9, 138.7, 143.8, 146.2, 164.5, 190.1.

ESMS (m/z) $[M+H]^+$: 396.111 (Calcd. 395.091).

N-(4-(3-(4-bromophenyl)acryloyl)phenyl)-4-methylbenzenesulfonamide (3g)

Pale Yellow solid; yield 85%, Rf 0.65 (30% EtOAc:Hexane), mp 194-195°C

IR: 3198 (NH), 1678 (C=O), 1390 & 1112 (SO2 asymm. & unsymm.) cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δppm: 2.5(s, 3H, -CH_3Ph), 7.17-8.7 (m, 14H, Ar-H, CH=CH), 10.82 (s, 1H, NH)

^{13}C NMR (100 MHz, CDCl3): 23.2, 115.1, 116.9, 122.3, 126.5, 128.8, 129.6, 131.3, 131.8, 132.1, 138.0, 138.9, 143.4, 147.2, 166.1, 189.6.

ESMS (m/z) $[M+H]^+$: 457.518 (Calcd. 455.0191)

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