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Synthesis, Characterization and Antioxidant Study of Some Novel Chalcones Carrying Sydnone Moiety

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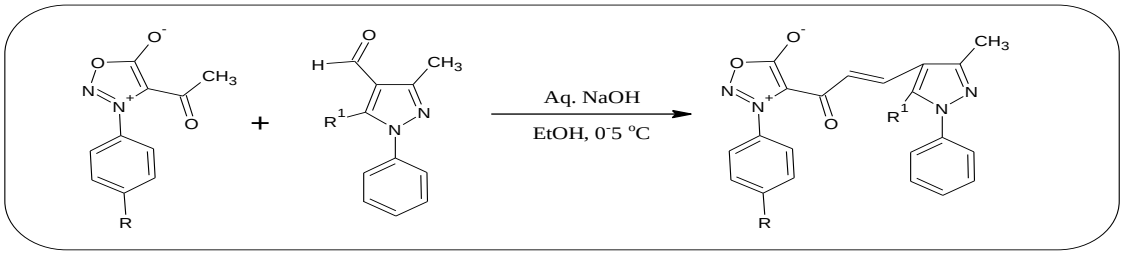
ABSTRACT

A novel series of 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one derivatives were synthesized by reacting different acetyl sydnone with various pyrazole aldehyde. The structures of the newly synthesized compounds were elucidated by spectral, analytical and X-ray crystallographic study. The newly synthesized compounds were also screened for their antioxidant property.



Keywords: Chalcone, DPPH scavenging assay, Pyrazoles, Sydnones

INTRODUCTION

Chalcones are the precursors of flavonoids and isoflavonoids and are found abundant in edible plants. They exhibit variety of pharmacological activities such as anti-inflammatory [1,2], antibacterial [3], antitumor [4], antifungal [5,6], antioxidant [7,8], immunosuppressive and antinociceptive properties [9,10].

Sydnones have attracted researchers because of their variety of pharmacological activity such as antitumor [11], anti-inflammatory [12], antibacterial [13], antifungal, antimicrobial [14], antiviral [15] etc., similarly, pyrazole-based derivatives have shown several biological activities such as antibacterial [16], antifungal, anti-inflammatory [17], antitubercular, anticancer [18], analgesic [19], antipyretic, anticonvulsant [20] activities.

Prompted by these observations and in continuation of our search for novel chalcones with enhanced biological activity [21], it was planned to synthesize a novel series of chalcones carrying both sydnone and pyrazole moiety and to evaluate their biological activity. So in this paper we report the synthesis of a novel series of 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one by the Claisen-Schimdt condensation of 4-acetyl-3-arylsydnone with 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-carbaldehyde in presence of base catalyst. The structure of these compounds was confirmed by Nuclear Magnetic Resonance (NMR), X-ray Diffraction (XRD) and mass spectral analysis. The compounds were also screened for their antioxidant activity.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes in Innovative DTC-967A digital melting point apparatus and are uncorrected. IR spectra were recorded by dispersing the compounds in KBr pellets on a Schimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance II NMR spectrometer and all the chemical shift values were reported as δ (ppm), downfield from TMS and proton signals are indicated as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were recorded on LCMS (SHIMADZU LCMS-8030) operating at 70 eV. The X-ray diffraction measurements were carried out in Rigaku Saturn 724+diffractometer. The purity of the compounds was checked by Thin Layer Chromatography (TLC) on silica gel plates.

The starting materials namely 2-acetyl-3-arylsydnone (1) and 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol carbaldehydes (2) were prepared as per the procedures reported in our earlier papers [21,22].

General procedure for the synthesis of 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one (3a-l)

4-Acetyl-3-arylsydnone (1) (0.1 mol) was suspended in 10 ml ethanol and cooled to 5-10°C. A solution of sodium hydroxide (0.4 N, 10 ml) was added slowly with stirring. To this mixture appropriate aldehyde (2) (0.1 mol) was added. The reaction mixture was stirred for 1 h at room temperature. The yellow precipitate was separated out and recrystallized with acetone to afford (3). The spectral data of the few representative compounds are given below.

1-(3-p-Tolylsydnon-4-yl)-3-(5-o-cresyloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3a

IR (KBr) γ/cm^{-1}: 1764 (Sydnone C=O), 1656 (α-β-unsaturated C=O), 1591 (C=C), ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.4 (s, 3H, o-cresyloxy -CH_3), 2.46 (s, 3H, p-tolyl -CH_3), 2.53 (s, 3H, pyrazole -CH_3), 6.45 (d, 1H, CH=CH, J=6.76 Hz), 7.24 (d, 1H, CH=CH, J=6.8 Hz), 6.9-7.6 (m, 13H, Ar-H). LC-MS: m/z: 492.70 (M^++1), (M.F. $C_{29}H_{24}N_4O_4$).

1-(3-p-Anisylsydnon-4-yl)-3-(5-o-cresyloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3b

(IR (KBr) γ/cm^{-1}): 1759 (Sydnone C=O), 1656 (α-β-unsaturated C=O), 1587 (C=C), ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.41 (s, 3H, o-cresyloxy -CH_3), 2.53 (s, 3H, pyrazole -CH_3), 3.87 (s, 3H, OCH_3), 6.45 (d, 1H, CH=CH, J=6.72 Hz), 7.08 (d, 1H, CH=CH, J=6.92 Hz), 7.2-7.6 (m, 13H, Ar-H). LC-MS: m/z: 508.70 (M^++1), (M.F. $C_{29}H_{24}N_4O_5$).

1-(3-p-Tolylsydnon-4-yl)-3-(5-(2, 4-dichlorophenyloxy)-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3d

IR (KBr) γ/cm^{-1}: 1762 (Sydnone C=O), 1656 (α-β-unsaturated C=O), 1589 (C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.47 (s, 3H, p-tolyl -CH_3), 2.55 (s, 3H, pyrazole -CH_3), 6.49 (d, 1H, CH=CH, J=8.88 Hz), 6.98 (d, 1H, CH=CH, J=8.84 Hz), 7.2-7.6 (m, 12H, Ar-H). LC-MS: m/z: 546.55 (M^++1), (M.F. $C_{28}H_{20}Cl_2N_4O_4$).

1-(3-p-Anisylsydnon-4-yl)-3-(5-(2,4-dichlorophenyloxy)-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3e

IR (KBr) γ/cm^{-1}**:** 1763 (Sydnone C=O), 1652(α-β-unsaturated C=O), 1585(C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.54 (s, 3H, pyrazole -CH_3), 3.89 (s, 3H, OCH_3), 6.49 (d, 1H, CH=CH, J=8.84Hz), 6.98 (d, 1H, CH=CH, J=8.84 Hz), 7.0-7.6 (m, 12H, Ar-H). LC-MS: m/z: 562 (M^++1), (M.F. $C_{28}H_{20}Cl_2N_4O_5$).

1-(3-Phenylsydnon-4-yl)-3-(5-(2, 4-dichlorophenyloxy)-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3f

IR (KBr) γ/cm^{-1}**:** 1764 (Sydnone C=O), 1651(α-β-unsaturated C=O), 1585(C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.54 (s, 3H, pyrazole -CH_3), 6.48 (d, 1H, CH=CH, J=8.84Hz), 6.98 (d, 1H, CH=CH, J=8.84 Hz), 7.24-7.7 (m, 13H, Ar-H). LC-MS: m/z: 532.55 (M^++1), (M.F. $C_{27}H_{18}Cl_2N_4O_4$).

1-(3-Phenylsydnon-4-yl)-3-(5-(β-naphthyloxy)-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3i

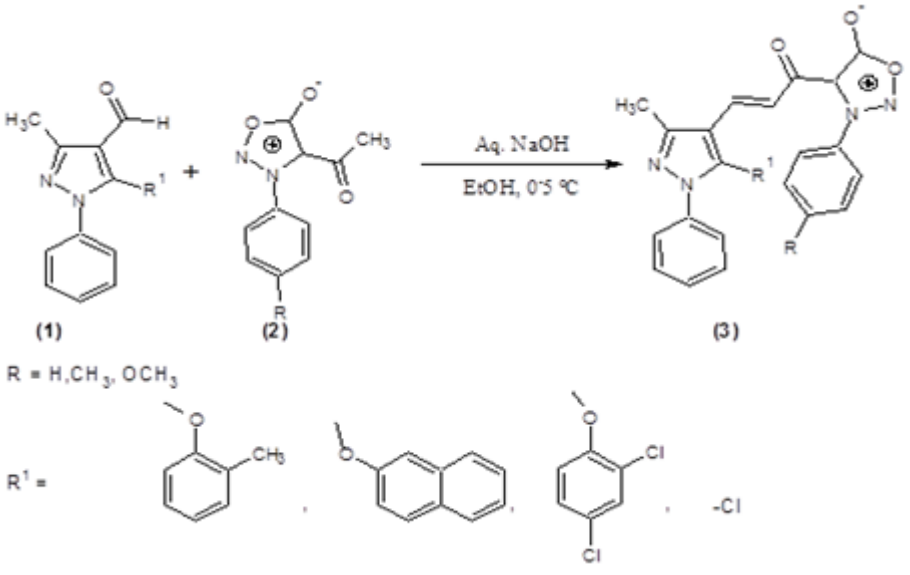
IR (KBr) γ/cm^{-1}: 1761 (Sydnone C=O), 1656(α-β-unsaturated C=O), 1591(C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.55 (s, 3H, pyrazole -CH_3), 6.5 (d, 1H, CH=CH, J=8.88Hz), 6.98 (d, 1H, CH=CH, J = 8.84 Hz), 7.24-7.69 (m, 17H, Ar-H). LC-MS: m/z: 514.53 (M^++1), (M.F. $C_{31}H_{22}N_4O_4$).

1-(3-p-Tolylsydnon-4-yl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3j

IR (KBr) γ/cm^{-1}: 1791 (Sydnone C=O), 1649(α-β-unsaturated C=O), 1583(C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.5 (s, 3H, p-tolyl -CH_3), 2.52 (s, 3H, pyrazole -CH_3), 7.74 (d, 1H, CH=CH, J=15.88 Hz), 7.86 (d, 1H, CH=CH, J=15.96 Hz), 7.4-7.44 (m, 5H, Ar-H of pyrazole phenyl), 7.48 (d, 2H, o-protons of sydnone tolyl, J=9.68 Hz), 7.54 (d, 2H, meta protons of sydnone tolyl, J=9.68 Hz). LC-MS: m/z: 420.75 (M^++1), 422.75 (M^+3) (M.F. $C_{22}H_{17}ClN_4O_3$).

1-(3-Phenylsydnon-4-yl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one 3l

IR (KBr) γ/cm^{-1}: 1788 (Sydnone C=O), 1653(α-β-unsaturated C=O), 1591(C=C). ^{1}H-NMR (400MHz) ($CDCl_3$) δ: 2.52 (s, 3H, pyrazole -CH_3), 7.74 (d, 1H, CH=CH, J=15.92 Hz), 7.86 (d, 1H, CH=CH, J=15.92 Hz), 7.42-7.72 (m, 10H, Ar-H). LC-MS: m/z: 406.75 (M^++1), 408.75 (M^+3) (M.F. $C_{21}H_{15}ClN_4O_3$) (Scheme 1).



Scheme 1: Synthetic scheme for the synthesis of chalcones

Antioxidant studies

The newly synthesized chalcones (3) were evaluated for their antioxidant property. Free radical scavenging activity of the test compounds were carried based on the scavenging activity of stable 2,2-diphenyl-1-picrylhydrazyl (DPPH). 100 µg/ml of each test sample and standard BHA was taken in different test tubes and the volume was adjusted to 1 ml using MeOH. Freshly prepared 1 ml of 0.1 mM DPPH solution was mixed and vortexed thoroughly and left in dark for 30 min. The absorbance of stable DPPH radical was measured at 517 nm. The DPPH control (containing no sample) was prepared using the same procedure. Radical scavenging activity was expressed as the inhibition percentage and was calculated using the equation of DPPH radical scavenging activity.

$$\text{DPPH radical scavenging activiy (\%)} = \frac{\text{(Abs Control - Abs Sample)}}{\text{(Abs Control)}} \times 100$$

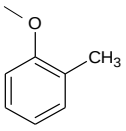
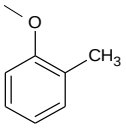
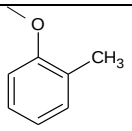
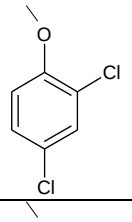
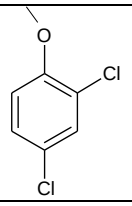
Where, Abs Control is the absorbance of DPPH radical+methanol; Abs Sample is the absorbance of DPPH radical+test sample/standard BHA. The DPPH scavenging activity for tested compounds showed activity ranging from 40.1%,-3.56%, whereas standard drug BHA showed 88% inhibition. Compound 3l, 3k and 3j displayed moderate radical scavenging activity i.e. 40.1%, 37.0% and 22.0% respectively among the set of compounds tested in the present study.

RESULTS AND DISCUSSION

Chemistry

A novel series of twelve chalcones (3) were prepared by the reaction of equimolar amounts of 2-acetyl-3-arylsydnone with different pyrazole carbaldehydes in ethanol medium at 0-5C in presence of base. Three different 2-acetyl-3-aryllsydnone and four different pyrazole aldehyde derivatives were employed in the present work. Structures of newly synthesized chalcones derivatives were confirmed on the basis of spectral and analytical data. Characterization data of these compounds are given in Tables 1-3. In the NMR spectrum of 1-(3-p-tolylsydnon-4-yl)-3-(5-o-cresyloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one (3a) the methyl protons attached to o-cresyloxy appeared as a singlet at δ-2.4, while the CH_3 protons of tolyl moiety came into resonance as a singlet at δ-2.46, while the methyl group attached to pyrazole ring appeared as singlet at δ-2.53. The olefinic protons came into resonance as two doublets at δ-6.45 (J=6.76 Hz) and 7.24 (J=6.8 Hz) integrating for one proton each. The signals due to aromatic protons overlapped with each other and appeared as multiplet in the region of δ-6.9-7.6 integrating for thirteen protons. In the IR spectrum of 1-(3-p-Tolylsydnon-4-yl)-3-(5-o-cresyloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one (3a) the absorption bands corresponding to C=O stretching was seen at 1656 cm^{-1} and C=C stretching frequency was observed at 1591 cm^{-1}. The ORPET view of single crystal X-ray analysis of 3a however confirmed that in the crystalline state the propenone has *Trans* geometry (Figures 1 and 2).

Table 1*:* Characterization data of 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one (3a-l)

Compound No.	R	R^1	M.P (°C) (Yield %)	Molecular formula (Mol. Wt)	% Analysis found (Calculated)		
					C	H	N
3a	CH_3		192-194 (75)	$C_{29}H_{24}N_4O_4$ (492)	70.68 (70.72)	5.02 (4.91)	11.37 (11.38)
3b	OCH_3		180 (44)	$C_{29}H_{24}N_4O_5$ (508)	68.51 (68.49)	4.83 (4.76)	10.98 (11.02)
3c	H		180-181 (47)	$C_{28}H_{22}N_4O_4$ (478)	70.21 (70.28)	4.66 (4.63)	11.65 (11.71)
3d	CH_3		208-210 (25)	$C_{28}H_{20}Cl_2N_4O_4$ (546)	61.40 (61.44)	3.71 (3.68)	10.16 (10.24)
3e	OCH_3		210-212 (30)	$C_{28}H_{20}Cl_2N_4O_5$ (562)	59.71 (59.69)	3.61 (3.58)	9.88 (9.94)

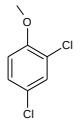
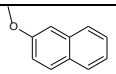
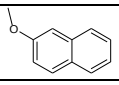
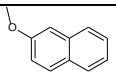
3f	H		184 (29)	$C_{27}H_{18}Cl_2N_4O_4$ (532)	60.91 (60.80)	3.43 (3.40)	10.41 (10.50)
3g	CH_3		222-224 (58)	$C_{32}H_{24}N_4O_4$ (528)	72.68 (72.72)	4.61 (4.58)	10.56 (10.60)
3h	OCH_3		196-198 (62)	$C_{32}H_{24}N_4O_5$ (544)	70.61 (70.58)	4.38 (4.44)	10.26 (10.29)
3i	H		241 (64)	$C_{31}H_{22}N_4O_4$ (514)	72.41 (72.36)	4.28 (4.31)	10.82 (10.89)
3j	CH_3	Cl	215 (41)	$C_{22}H_{17}ClN_4O_3$ (420)	62.82 (62.79)	4.05 (4.07)	13.29 (13.31)
3k	OCH_3	Cl	193-194 (54)	$C_{22}H_{17}ClN_4O_4$ (436)	60.53 (60.49)	3.88 (3.92)	12.88 (12.83)
3l	H	Cl	216-217 (43)	$C_{21}H_{15}ClN_4O_3$ (406)	62.08 (62.00)	3.68 (3.72)	13.74 (13.77)

Table 2: Crystal data and structure refinement for chalcone 3a

Identification code	**3a**
Empirical formula	$C_{29}H_{24}N_4O_4$
Formula weight	492.52
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	12.9021(10)
b/Å	7.6076(8)
c/Å	25.311(2)
α/°	90
β/°	95.338(8)
γ/°	90
Volume/$Å^3$	2473.6(4)
Z	4
$\rho_{calc}g/cm^3$	1.323
μ/mm^{-1}	0.090
F(000)	1032.0
Radiation	MoKα (λ=0.71073)
2Θ range for data collection/°	4.312-50.054
Index ranges	$-15 \leq h \leq 15, -9 \leq k \leq 8, -30 \leq l \leq 30$
Reflections collected	23787
Independent reflections	4360 [R_{int}=0.0919, R_{sigma}=0.0640]
Data/restraints/parameters	4360/0/337
Goodness-of-fit on F^2	1.077
Final R indexes [I > =2σ (I)]	R_1=0.0816, wR_2=0.1787
Final R indexes [all data]	R_1=0.1263, wR_2=0.2094
Largest diff. peak/hole/e $Å^{-3}$	0.23/-0.22

Table 3: DPPH scavenging activity of compounds (3a-l)

Compounds	**DPPH assay %**
3a	5.63
3b	7.2
3c	7.0
3d	7.7
3e	3.56
3f	7.1
3g	16.2
3h	7.0
3i	18.0
3j	22.0
3k	37.0
3l	40.1

Figure 1: ORTEP of 3a chalcone

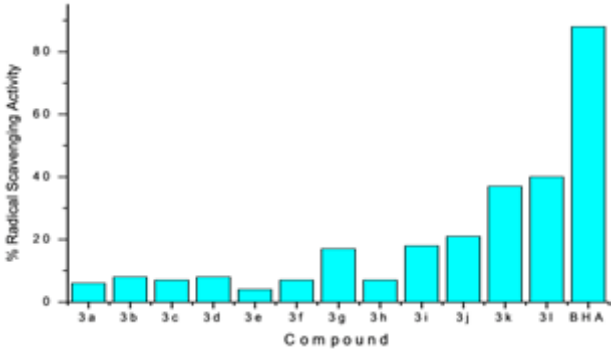


Figure 2: DPPH scavenging assay of the compounds (3a-l)

CONCLUSION

In this study, a series of novel 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one were prepared. The newly synthesized chalcones were screened for their anti-oxidant activity.

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