SYNTHESIS OF 5-(4'-AROYL)-ARYLOXY METHYL-4H-(1,2,4)-TRIAZOLIN-3-THIOL AND THEIR BIOLOGICAL ACTIVITY

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Abstract: 5-(4'-aroyl)-aryloxy methyl-4H-1,2, 4)-triazolin-3-thiols were synthesized by using substituted phenyl benzoates as the starting material. Phenyl benzoates on Fries rearrangement gave p-hydroxy benzophenones which on treatment with ethyl bromoacetate in presence of anhydrous potassium carbonate and dry acetone gave corresponding benzoyl phenyloxy esters in excellent yield. Esters were refluxed with thiosemicarbazide in presence of acetic anhydride gave cyclized title compounds. Supports for the structures of the synthesized compounds have been provided by their elemental analysis and spectral data. The newly synthesized compounds were screened for antibacterial and antifungal activities.
Key words: Aroyl aryloxy esters, triazolin-3-thiols.

Introduction

Compounds containing triazole ring are known to possess interesting properties such as antitubercular[1], bacteriostatic[2], hypoglycemic[3-5], diuretic[6], antiviral[7] and antifungal activities.[8-9] Substituted 1,2,4-triazoles have received considerable attention during the last two decades as potential biologically active agents.[10-13]

In view of these observations we have synthesized 5-(4'-aroyl)-aryloxy methyl-4H-1,2,4)-triazolin-3-thiols and evaluated them for antifungal and antibacterial activity.

The substituted p-hydroxy benzophenones **1a-d** were synthesized by the benzoylation of phenols followed by Fries rearrangement.[14-15] Their structural elucidations were confirmed by IR and ^{1}H NMR data.

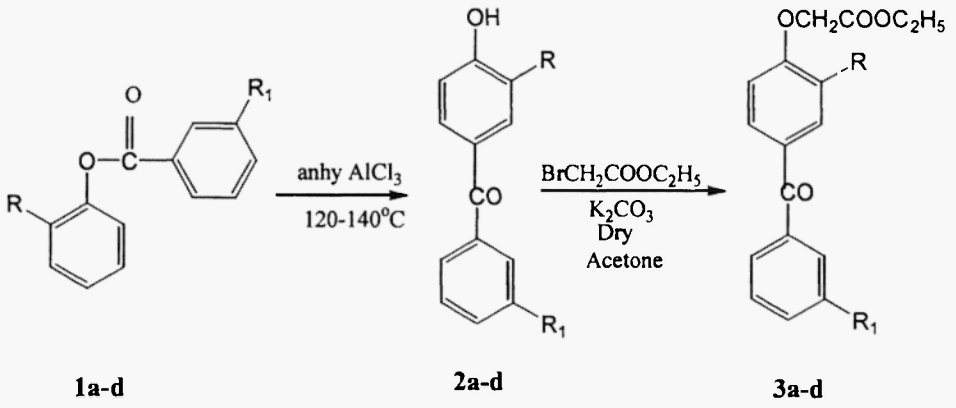
p-Hydroxy benzophenones **2a-d** on treatment with ethyl bromoacetate in presence of anhydrous potassium carbonate and dry acetone gave corresponding benzoyl phenoxy esters **3a-d** in excellent yield.[16] The compound **3a** showed IR absorption at 1751 cm^{-1} assigned to ester carbonyl and at 1641 cm^{-1} assigned to aromatic carbonyl group. ^{1}H NMR spectrum of **3a** showed a triplet centered at δ 1.3 assigned to methyl group, a quartet centered at δ 4.25 assigned to methylene protons of ester, a singlet at δ 4.63 assigned to methylene protons lying in between phenoxy and ester group and a broad multiplet at δ 6.8 to 7.8 assigned to aromatic protons.

Esters **3a-d** were refluxed with thiosemicarbazide in the presence of polyphosphoric acid gave cyclized compounds **4a-d**. the compound **4a** showed IR absorption peak at 2600 cm^{-1} assigned to S-H, 1596 cm^{-1} assigned to C=N and at 3021 cm^{-1} assigned to Ar-H. ^{1}H NMR spectrum of **4a** showed a singlet at δ2.23 assigned to methyl group, a singlet at δ 4.6 assigned to methylene protons a broad multiplet at δ 6.8 to 7.8 assigned to aromatic protons, a broad singlet at δ 8.9-9.1 due to NH and a singlet at δ 9.4 due to SH.

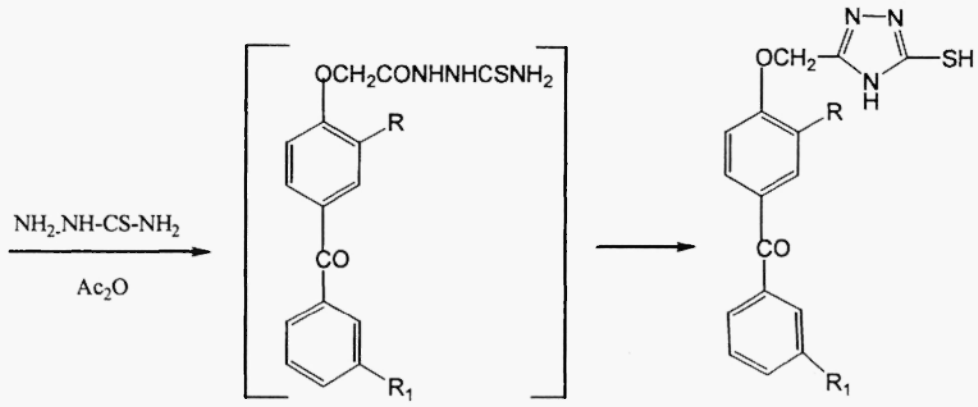
Structures of all the new compounds synthesized were established by their elemental analysis (Table – I) and spectral data.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activities against E.Coli, P.aeruginosa and S.aureus by the disk diffusion method. The test compounds were dissolved in dimethyl formamide and different aliquots were placed in each cup. Incubation was carried out at 37°C for 24 hr. Chloromycetin was used as the standard drug. The diameters of zone of inhibition was measured for 10μg/ml concentration. From the antibacterial activity data, it was found that most of the compounds were moderately active against micro organisms. Antifungal activity was tested against Aspergillus niger and Aspergillus flavus by the standard methods using Nystatin as a standard drug. The results are summarized in Table-II.



1a-d **2a-d** **3a-d**



4a-d

a: R=H, R_1 = H

b: R=CH_3, R_1 = H

c: R=H, R_1=Cl

d: R=CH_3, R_1=Cl

SCHEME-1

TABLE - I

Compd. No.	Yield (%)	m.p in °C	Analysis (%) Found (Calculated) C	H	Cl	S	N	IR(nujol) cm^{-1}	^1H NMR ($CDCl_3$)
2a	80	130-2	78.77 (78.79)	5.03 (5.05)	-	-	-	1641(C=O) 3200(O-H)	6.8 -7.8(bm, 9H. Ar-H), 9.8 (s, 1H, OH)
2b	90	140-1	79.22 (79.24)	5.64 (5.66)	-	-	-	1635 (C=O) 3150(O-H)	6.9 -7.9(bm, 9H, Ar-H), 9.9 (s, 1H, OH)
2c	85	128-9	67.07 (67.09)	3.85 (3.87)	15.22 (15.26)	-	-	1645 (C=O) 3250(O-H)	6.6 -7.8(bm, 8H, Ar-H), 9.85 (s, 1H, OH)
2d	95	137-8	68.11 (68.15)	4.9 (4.89)	14.38 (14.40)	-	-	1636 (C=O) 3170(O-H)	6.75 -7.8(bm, 8H, Ar-H), 9.73 (s, 1H, OH)
3a	85	72-3	71.80 (71.83)	5.66 (5.63)	-	-	-	1751(ester, C=O), 1641 (Ar C=O)	1.3(t,3H,CH_3), 4.25(q,2H,CH_2), 4.63 (s, 2H, OCH_2), 6.8 -7.8(bm, 9H. Ar-H),
3b	85	56-7	72.46 (72.48)	6.06 (6.04)	-	-	-	1755(ester, C=O), 1645 (Ar C=O)	1.2(t,3H,CH_3).2.23(s.3H,ArCH_3) 4.2(q,2H,CH_2), 4.62 (s, 2H, OCH_2), 6.8 -7.8(bm, 8H, Ar-H),
3c	85	76-7	64.06 (64.05)	4.68 (4.71)	11.18 (11.15)	-	-	1758(ester, C=O), 1646 (Ar C=O)	1.2 (t.3H,CH_3), 4.2 (q,2H,CH_2). 4.61 (s, 2H, OCH_2), 6.7 -7.8(bm, 8H, Ar-H),
3d	80	73-4	64.96 (64.96)	5.12 (5.11)	10.69 (10.68)	-	-	1753(ester, C=O), 1644 (Ar C=O)	1.3(t,3H,CH_3).2.21(s.3H,ArCH_3). 4.22(q,2H,CH_2), 4.6 (s, 2H. OCH_2). 6.6 -7.8(bm. 7H. Ar-H).
4a	65	202-4	61.72 (61.74)	4.16 (4.18)	-	10.27 (10.29)	13.2 (13.5)	1596 (C=N),1644 (Ar C=O), 2600 (S-H)	4.5 (s.2H.OCH_2), 7.0-7.8 (bm.9H.Ar H), 8.9-9.1 (bs.1H.NH). 9.4 (s,1H.SH)
4b	68	217-8	62.75 (62.77)	4.60 (4.61)	-	9.83 (9.85)	12.90 (12.92)	1598 (C=N),1646 (Ar C=O), 2610 (S-H)	2.21(s,3H,ArCH_3), 4.4 (s,2H,OCH_2), 7.1-7.8 (bm,8H,Ar H), 8.8-9.0 (bs.1H,NH), 9.6 (s.1H.SH)
4c	70	225-6	55.55 (55.57)	3.45 (3.47)	10.25 (10.27)	9.24 (9.26)	12.14 (12.16)	1590 (C=N),1640 (Ar C=O). 2596 (S-H)	4.45 (s,2H,OCH_2), 7.2-7.9 (bm.8H.Ar H). 8.8-9.1 (bs.1H.NH). 9.45 (s.1H.SH)
4d	60	221-3	62.94 (62.96)	4.30 (4.32)	10.94 (10.96)	9.86 (9.88)	12.94 (12.96)	1598(C=N),1638 (Ar C=O), 2592 (S-H)	2.2 (s,3H,ArCH_3), 4.5 (s,2H.OCH_2). 7.1-7.8 (bm,7H,Ar H), 8.9-9.1 (bs,1H,NH). 9.4 (s.1H,SH)

TABLE – II

Antimicrobial activity of representative Compounds 4a-d

Compound	Antibacterial activity E.coli	P. aeruginosa	S.aureus	Antifungal activity A.niger	A.flavus
4a	++	+	++	++	++
4b	++	++	+	+	+
4c	++	+	++	++	++
4d	++	++	+	++	+
control DMF	-	-	-	-	-

zone diameter of growth inhibition : <10mm (-)
10-12 m (+), 13-15 mm (+ +), 16-20 m (+ + +)
Chloromycetin (+ + +), Nystatin (+++)

Experimental section

Melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Shimadzo FT-IR spectrophotometer in nujol. ^{1}H NMR spectra were recorded on a Hitachi R-600 spectrometer with TMS as internal standard.(Table –I).

General procedure for the preparation of p-hydroxy benzophenones, 2a-d. A typical procedure is described for the preparation of **p-hydroxy benzophenone (2a):** A mixture of phenyl benzoate **1a** (1.98g, 0.01mol) and anhydrous Aluminium Chloride (1.88g, 0.01mol) were ground well and heated slowly on an oil bath. The temperature of the reaction mixture was raised to 120-140°c and maintained constantly for 15 minutes. The reaction mixture was cooled and poured into crushed ice(100g) and 6N HCl (20ml).The pasty mass obtained was subjected to column chromatography using hexane :chloroform : acetone (7:2:1) to separate ortho and para isomers (10:90). The para isomer was recrystallised from ethanol to give **2a** as white crystalline solid.

General procedure for the preparation of aroyl aryloxyacetic ester, 3a-d. A typical procedure is described for the preparation of **ethyl-4-benzoyl phenyloxyacetate (2a):** A mixture of 4-hydroxy benzophenone **2a** (1.98g, 0.01 mol) and ethyl bromoacetate (1.65g, 0.01 mol) in dry acetone (50 ml) and potassium carbonate (4g, 0.03 mol) were refluxed for 6 hr. To the cooled reaction mixture, water (25ml) was added and extracted with ether (3x25 ml). The ether layer washed with 5% aqueous sodium hydroxide (3x10 ml) and with water (2x10ml) and dried over anhydrous sodium sulphate and evaporated. The crude product was recrystallised from ethanol to give **3a** as white crystalline solid.

General procedure for the preparation of 5-(4'-aroyl)-aryloxy methyl-4H-(1, 2, 4)-triazolin-3-thiol, 4a-d. A typical procedure is described for the preparation of 5-(4'-benzoyl)-phenoxy methyl-4H-(1,2,4)-triazolin-3-thiol. A mixture of ester 3a (2.84g, 0.01 mol) and thiosemicarbazide (1.01g, 0.01 mol) and acetic anhydride (25ml) were refluxed for about 3 hrs. The reaction mixture was poured into ice cold water (50ml). The compound was extracted with ether (2x25ml) and washed with water (2x25ml), dried over anhydrous sodium sulphate and then evaporated. The solid was recrystallised from alcohol to get white crystalline solid of 4a.

Conclusion

In conclusion we have shown that the cyclization of aroyl aryloxyacetic ester, **3a-d** with thiosemicarbazide in the presence of acetic anhydride gave 5-(4'-aroyl)-aryloxy methyl-4H-(1,2,4)-triazolin-3-thiol, **4a-d**. The newly synthesized compounds have shown moderate antimicrobial activity and the results are summarized in (TABLE II).

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