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SYNTHESIS OF SUBSTITUTED BROMO-NITRO-CHALCONES AND 3, 5-DIARYL-Δ^2- ISOXAZOLINES

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ABSTRACT

Five different substituted chalcones (I_{a-e}) were synthesized by condensing 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone with five different aromatic aldehydes in ethanol using 40% NaOH. These chalcones were cyclized with hydroxylamine hydrochloride in pyridine containing few drops of piperidine yielding 3, 5-diaryl-Δ^2- isoxazolines (II_{a-e}). The synthesized compounds were characterized by IR and ^{1}H NMR spectral analysis.

Key words: Synthesis, Bromo-nitro-chalcones, Bromo-nitro isoxazolines.

INTRODUCTION

Chalcones are well-known intermediates for synthesis of various heterocyclic compounds. The compounds with the backbone of chalcones have been reported as posses various antimicrobial[1], anti-inflammatory[2], analgesic[3], anticancer[4], antitubercular[5]. It was noticed that among the recently published chalcones possessing antimicrobial activity, several are para-nitrosubstituted derivatives[6-9]. The main method for synthesis of chalcones is the classical Claisen-Schmidt condensation of substituted aromatic ketone and substituted aldehydes in alkaline bases[10]. This on cyclization with hydroxylamine hydrochloride in alkaline medium gives the corresponding isoxazolines derivatives.

In recent years attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remains a main focus of medicinal research. The compounds with isoxazoline structures are known to possess a wide spectrum of activities like antidepressant[11],

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antibacterial[12], antifungal, anticancer, antiviral, and insecticidal are also important precursor for different natural products[13-16]. In fact valdecoxib is an isoxazoline derivatives now widely used in the market as an anti-inflammatory drug[17].

EXPERIMENTAL

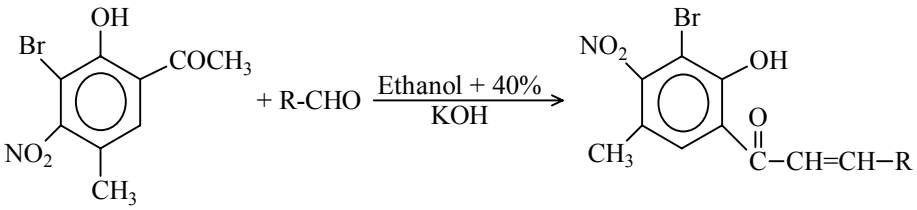
Melting points of all synthesized compounds were determined in open capillary tube M.P. apparatus and are uncorrected. Chemicals and solvents were of highest purity commercially available. The purity of synthesized compounds were checked by the using silica G. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker AVANCE II 400 NMR spectrometer with TMS as internal standard. I.R. were recorded on Perkin-Elmer-841 spectrometer in KBr disc.

Synthesis of 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I)

p-cresyl acetate was prepared by known method. Then by fries migration 2-hydroxy-5-methyl acetophenone was obtained. This on bromination gives 2-hydroxy-3-bromo-5-methyl acetophenone, which further on nitration gives starting compound i.e. 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I).

General method for synthesis of bromo-nitro substituted Chalcones (I_{a-e})

These compounds (I_{a-e}) were synthesized from 2-hydroxy-3-bromo-4-nitro-5-methyl acetophenone (I) 0.01 M by reacting it with five different aromatic aldehydes (0.01 M) by reported method in ethanol using 40% KOH. The physical data of compounds (I_{a-f}) are given in Table 1.

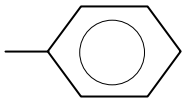
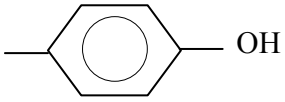
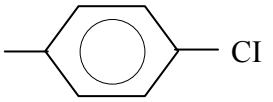
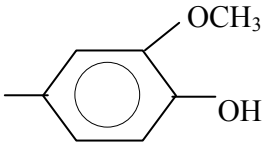
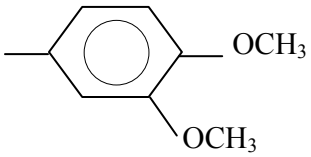


(I) **(Ia-e)**

Scheme 1

The groups R are given in Table 1.

Table 1: Physical data of Compounds (I_{a-e})

Compound No.	R	Mol. Formula	M.P. (^oC)	Yield (%)
I_a		$C_{16}H_{12}BrNO_4$	150	75
I_b		$C_{16}H_{12}BrNO_5$	95	73
I_c		$C_{16}H_{11}BrClNO_4$	140	78
I_d		$C_{17}H_{14}BrNO_6$	105	71
I_e		$C_{18}H_{16}BrNO_6$	150	68

Characterization of Compound I

IR (KBr) cm^{-1}: 2923 (hydrogen bonded Ar –OH), 1638 (C = O stretching), 1310 (Ar-O stretching), 1558 and 1343 (-NO_2 stretching), 554 (C-Br).

^{1}H NMR ($CDCl_3$) Data: δ 2.3 (s, 3H, Ar-CH_3), 2.7 (s, 3H, Ar-CO-CH_3), 7.6 (s, 1H, Ar-H), 12.5 (s, 1H, Ar-OH).

Characterization of Compound (I_c)

IR (KBr) cm^{-1}: 2917 (hydrogen bonded Ar –OH), 2670 (Ar-H stretching), 1639 (-C = O stretching), 1562 and 1388 (-NO_2 stretching), 819 (para substituted ring), 1234 (-C-O of phenol), 554 (-C-Br), 644 (-C-Cl stretching).

^{1}H NMR ($CDCl_3$) Data: δ 2.3 (s, 3H, Ar-CH_3), 7.4 (dd, 1H, = CH_A), 7.6 (dd, 1H, = CH_B), 7.8-8 (m, 5H, Ar-H), 12.2 (s, 1H, Ar-OH).

Characterization of Compound (I_e)

IR (KBr) cm^{-1}: 3339 (Ar –OH), 2920 (Ar-H, C-H stretching), 2842 (Aliphatic C-H stretching of CH_3), 1635 (-C = O stretching), 1560 and 1383 (-NO_2 stretching), 1264 (-C-O of phenol), 1607 (-C=C-), 575 (-C-Br), 828 and 861 (para substituted ring).

^{1}H NMR ($CDCl_3$) Data: δ 2.2 (s, 3H, Ar-CH_3), 3.8 (s, 3H, Ar-OCH_3 m), 3.9 (s, 3H, Ar-$0CH_3$ p), 6.8 (d, 1H, = CH_A), 6.9 (d, 1H, = CH_B), 7.0-7.9 (m, 4H, Ar-H), 12.7 (s, 1H, Ar-OH).

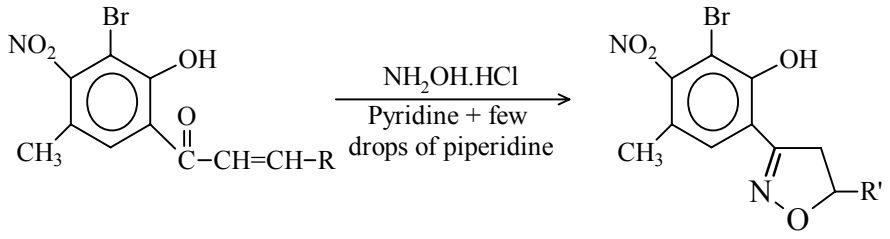
Characterization of Compound (I_b)

IR (KBr) cm^{-1}: 3392 (Ar –OH), 2921 (Ar-H, C-H stretching), 1636 (-C = O stretching), 1552 and 1359 (-NO_2 stretching), 1246 (-C-O of phenol), 551 (-C-Br), 866 (para substituted ring).

^{1}H NMR ($CDCl_3$) Data: δ 2.3 (s, 3H, Ar-CH_3), 6.9 (d, 1H, = CH_A), 7.9 (d, 1H, = CH_B), 7.2-7.7 (m, 5H, Ar-H), 12.8 (s, 1H, Ar-OH).

Synthesis of 3.5-diaryl isoxazolines (II_{a-e})

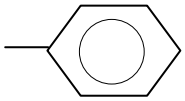
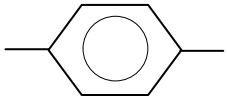
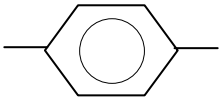
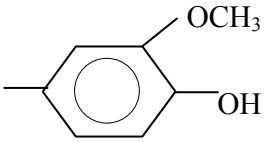
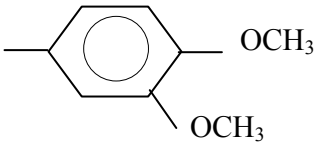
A mixture of bromo, nitro-substituted chalcone (0.01 M) and $NH_2OH.HCl$ (0.02 M) were refluxed in 20 mL pyridine containing few drops of piperidine for 3-4 hours. Cooled and acidified with 1 : 1 ice cold HCl, Thus compounds (II_{a-e}) were synthesized and recrystallised. Physical data for those compounds are shown in Table 2.



(Ia-e) **(IIa-e)**

Scheme II

Table 2: Physical data of the compounds (II_{a-e})

Compound No.	R	Mol. Formula	M.P. (°C)	Yield (%)
II_a		$C_{16}H_{13}BrN_2O_4$	150	75
II_b		$C_{16}H_{13}BrN_2O_5$	175	73
II_c		$C_{16}H_{12}BrClN_2O_4$	120	72
II_d		$C_{17}H_{15}BrN_2O_6$	195	68
II_e		$C_{18}H_{17}BrN_2O_6$	160	69

Characterization of Compound (II_c)

IR (KBr) cm^{-1}: 3394 (Ar-OH stretching), 2918 (Ar-C-H), 1560 and 1385 (-NO_2), 1616 (-CH_2 of iso ring), 1740 (-C = N), 1260 (=N-O), 575 (C-Br), 692 (C-Cl), 820 (para substituted ring).

^{1}H NMR ($CDCl_3$) Data: δ 2.3 (s, 3H, Ar-CH_3), 3.4 (dd, 1H, CH_A), 4.3 (dd, 1H, CH_B), 5.2 (dd, 1H, CH_X), 6.8-7.6 (m, 5H, Ar-H), 12.2 (s, 1H, Ar-OH).

Characterization of Compound (II_e)

IR (KBr) cm^{-1}: 3395 (Ar-OH stretching), 2917 (Ar-C-H), 2848 (Aliphatic –C-H), 1562 and 1383 (-NO_2), 1694 (-CH_2 of iso ring), 1636 (-C = N), 1186 (-C = N-O), 1264 (-C-O of phenol), 575 (C-Br).

^{1}H NMR ($CDCl_3$) Data: δ 2.2 (s, 3H, Ar-CH_3), 3.8 (s, 3H, Ar-OCH_3 m), 3.9 (s, 3H, Ar-$0CH_3$ p), 3.0 (dd, 1H, CH_A), 3.1 (dd, 1H, CH_B), 5.5 (dd, 1H, CH_X), 6.9-7.9 (m, 4H, Ar-H), 12.8 (s, 1H, Ar-OH).

RESULTS AND DISCUSSION

Thus the bromo-nitro-substituted chalcones (I_{a-e}) and 3,5-diaryl-Δ^2- isoxazolines were synthesized through the route as shown in reaction schemes. Physical data of compounds are shown in Table 1 and 2. The structure of synthesized compound (I), I_c, I_e, I_b and II_c, II_e were confirmed on the basis of I. R. and NMR spectral analysis.

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