SYNTHESIS OF 4-(4-ACETAMIDOBENZOYL) -2-OXIRANE CARBOXYLIC ACID AND SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS WITH NON-MIXED AND MIXED SYSTEM

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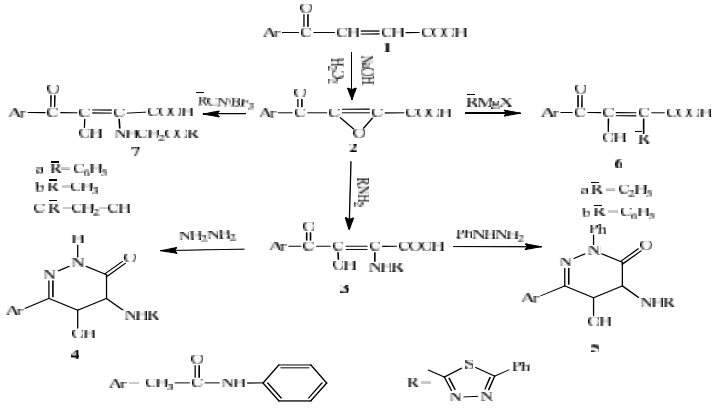
ABSTRACT

The present work deals with the reaction of 4-(4-Acetyl amino phenyl-4-oxobut-2-enoic acid (1) with hydrogen peroxide afforded oxirane derivative (2).The latter compound was treated with 2-amino – 5 – phenyl -1, 3, 4-thiadiazole to yield imidazole (3) .The new heterocyclic compounds(4,5) are used as a key starting materials, reaction of (2) with amines, hydrazines, active methylene compounds and Friedel—Crafts reactions have been studied to synthesize some hetrocycles include derivatives. Also, (2) reacted with acetic acid. The structure of the newly synthesized compounds were elucidated by elemental analysis andspectroscopic data.

INTRODUCTION

4-(4-acetylaminophenyl) -4-oxo-but -2 -enoic acid have been shown that the substitution pattern on the aroyl moiety influences the antipr- liferative activity[1]and they have activated double bond, Half waventhe behaviour of the oxirane ring towards different nitrogen and carbon nucleophiles and its behaviour towards the expected biological activity of some synthesized compoundstreatment of an alcoholic solution of chalcone (**1)** with hydrogen peroxide in alkaline medium yielde3-(4-acetamido-benzoyl) oxiran-2-carboxylic acidde (**2**) (Scheme 1).Previously it was reported [2] that epoxides underwent ring opening by action of Grignard reagents. So (**2**) was reacted

with ethyl magnesium bromide and phenyl magnesium bromide and afforded 4-(4-acetamidophenyl)-2-ethyl-3-hydroxy-4-oxobutanoic acid and 4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2-phenylbutanoic acid (**6a**, **6b**). These observations prompted us to carry out the conversion of α,β-epoxy ketone (**2**) into 2-oxazolines via the reaction with benzonitrile, acetonitrile, and acrylonitrile in the presence of boron triflourideetherate as catalyst yielding the corresponding α-hydroxy-β-amido derivatives (**7a**,**7b**,**7c**) 4-(4-acetamido phenyl)-3-hydroxy-4-oxo-2- (phenoxycarbonyl) amino) butanoic acid and 4-(4-acetamidophenyl)-3-hydroxy-2-((methoxycarbonyl)amino)-4-oxo butanoic acid 4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2- (vinyloxy) carbonyl) amino)butanoic acid , When compound **(3)** was allowed to react with hydrazine hydrate or phenyl hydrazine in boiling ethanol it yielded N-(4-(4-hydroxy-6-oxo-5- (5- phenyl-1, 3, 4-thiadinazol-2-yl) amino)-1, 4, 5, 6, tetrahydropyridazine or 1-phenylpyridazin-3-yl) phenyl) acetamide (**4** and **5**) respectively.



(Scheme 1)

RESULTS AND DISCUSSION

Reports from our laboratory[3-7] revealed that the β-aroyl acrylic acids are convenient poly electrophilic reagents in the synthesis of hetero- cycles , which for the addition reaction of nucleophililese.g.carbon ,nitrogen,sulfur occur exclusively at the α-carbon electrophilic center of the carboxy precursors. Morever , reaction with hydrogen peroxide afford oxirane derivative[8]. With the aim of the synthetic potential of β-aroyl acrylic acids ,the authors can be reported the behavior of 3-(4- acetylaminobenzoyl) prop -2- enoic acid (1) that was allowed to react hydrogen peroxide in the presence of sodium hydroxide afforded the epoxide product E-1-(4-acetylaminobenzoyl) 2-oxirane carboxylic acid (2). When the acid (2) is submitted to react with 5-aryl-2-amino-1,3,4-thiadiazole in the presence of few drops of piperidine afforded 2-(5-aryl-1,3,4- thiadiazol-2-yl)amino-3-hydroxy-3-(4-acetyl aminobenzoyl) propanoic acid 3, via the N- alkylation of amino thiadiazole moieties that added to the activated 3-membered heterocycle of the acid (2). The acids (3) undergo spontaneous dehydration . The different kinds of electrophilic centers in [9] the compounds 3 can be reacted with simply binucleophiles e.g. hydrazine derivatives to afford an important heterocycles . This can be affected on the reaction path that depends on stability of intermediate and the product. Thus, when the compounds (3) were allowed to react with phenyl hydrazine afforded the pyridazinone derivatives (4) and pyrrole derivatives (5). The latter compounds have low yield due to the steric phenyl group is outweigh intramolecular hydrogen bond and becomes a driving force to regioselective isomer (4). Previously it was reported [9] that epoxides underwent ring

opening by action of Grignard reagents. So, (2) was reacted with ethyl magnesium bromide and phenyl magnesium bromide and afforded 4-(4-acetamidophenyl)-2-ethyl-3-hydroxy-4-oxobutanoic acid and4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2-phenylbutanoic acid (6a, 6b). Also , the compounds 3 have been reacted with carbon [10] electrophiles derivatives (7a—7c), which underwent cyclization by subjection to fusion in an oil bath at 210-220◦ C and furnished

EXPERIMENTAL WORK

All melting points are uncorrected. Elemental analysis were carried out in the MicroanalyticalCenter, Cairo University, Egypt. **IR** spectra were recorded in (**KBr**) disks on Shimadzu **FTIR** 8101 PC and **^{1}H-NMR** spectra recorded on a Varian **300 MHz** in (**$CDCl_3$**) or (**DMSO-d_6**) as solvents, (Chemical shifts in δppm) using **TMS** as internal standard. The mass spectra were recorded on Shimadzu **GCMS-QP-1000EX** mass spectrometer at **70** e. v. Homogeneity of all compounds synthesized was checked **TLC**.

Synthesis of E-1-(4-acetylaminobenzoyl) 2-oxirane carboxylic acid (2)

A solution of acid (**1)** (2.33g;0.01 mol) in methanol (20mL) and acetone(20mL) was treated with 8% aqueous sodium hydroxide (12mL) and hydrogen peroxide (30% 10mL) drop by drop. The solution was shaken and heated for 2 h, then allowed to stand overnight at room temperature, water was then added and the solution acidified with dilute HCl. The mixture was extracted with ether and the solid separated was crystallized from the suitable solvent to give (**2)**The IR spectrum of (**2)** showed absorption bands at 1740— 1750 cm^{-1} ((CO), cyclic imides), 1670 cm^{-1}((CO), ketone),

1665 cm^{-1}((CO), amide), 1330 and 1120 cm^{-1} ((SD_2)), 1080 cm^{-1} ((C—O—C)), and 3160 cm^{-1} ((NH)). The mass spectrum showed peaks at m/z (relative intensity/%): 497.5 (0.20) (M+), 374 (0.50), 372 (0.11), 378 (0.19), 316 (2.17), 198, 183 (2.60), 168 (6.70), 141 (2.95), 140 (8.30), 91 (30.40), 77 (36.50), 75 (13.50), 65 (21.20).

Synthesis of 4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2-((5-phenyl-1, 3, 4-thiadiazol-2-yl)amino)butanoic acid (3)

A solution of oxirane derivative **(2)** (2.5g;0.01mol) and 5-phenyl -1, 3, 4-thiadiazol-2-yl-amine (1.77g; 0.01mol) in(30mL) ethanol was heated under reflux for 3h. The solid that separated after concentration and cooling was filtered off and crystallized from the suitable solvent to give (**3)** .Mp 191-194 C. IR(KBr) 1614 (C=N), 1660, 1670, 1675 (CO), 3246 (NH), 3415 (OH). ^{1}HNMR (DMSO): 2.6(s,3H,CH_3), 4.13(dd,1Ha, (J=15.4, J=11.4) and 1Hb (J=15.4, J=11.2) sterogenicmethine protons), 4.35 (bs,1H, OH proton of hydroxyl group), multiplet at 7.44 – 7.74 assigned ArH aromatic protons, singlet 14.4 acidic OH=NH proton, N 13.72; found: C 58.60, H 3.65, N 13.45. MS:m/z 408[M], 377[M-OH+CH_3], 285, 213, 141.

Synthesis of N-(4-(4-hydroxy-6-oxo-5-(5-phenyl1, 3, 4thiadina zol-2-yl)amino)-1, 4, 5, 6 tetrahydropyridazine or 1-phenylpyri dazine-3-yl) phenyl)acetamide (4,5)

A solution of acid (**3)** (2.2g;0.015mol) in ethanol(30mL) was treated with hydrazine hydrate or phenyl hydrazine (0. 01mol) and heated under reflux for 3 h. The solids that separated after concentration and cooling were crystallized, from the suitable solvent to give the pyridazinones (**4,5**) Its IR spectrum revealed strong absorption bands at 1603, 1630, 1687, 3272, 3440 cm^{-}

[1] attributable to υC=N, υmax of carbonyl groups υNH and υOH respectively. for **(5)** . The [1]H-NMR spectrum of compound (**4)** exhibits signals at δ ppm 2.5 (s, 3H H_3C CO), 4.6 (s, 2H, methine protons), 6.84-7.96 (m,9H ArH) 8.65- 9.98 (broad singlet 4H, NH and OH protons)exchangeable inD_2O).

Synthesis of -(4-acetamidophenyl)-2-ethyl-3-hydroxy-4-oxobutanoic acid and4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2-phenylbutanoic acid (6a, 6b)

To a suspension of epoxide **(2)** (0.01 mol) in dry ether (50 cm_3) an ethereal solution of ethyl magnesium bromide or phenyl magnesium bromide (0.03mol) was added, the reaction mixture was refluxed on a steam bath for 4h, then decomposed with a saturated solution of ammonium chloride and extracted with ether. The solid obtained was crystallized from the proper solvent. The structure of (**6a)** and (**6b)** was proved by IR spectrum which showed absorption bands at 3455 cm^{-1} (OH). 1H NMR spectrum of (**6a)** showed signals at: 1.4 (t, 3H, CH_2CH_3), 3.2 (d, 1H, α-CH), 3.4 (d, 1H, β-CH), 4.2 (q, 2H, CH_2CH_3), 4.6 (s, 2H, NCH_2CO), 7.3—7.8 (m, 12H, ArH), 9.3 (s,1H,CONH), 12.2 (s, 1H,OH).

Synthesis of 4-(4-acetamidophenyl)-3-hydroxy-4-oxo-2-((phenoxy carbonyl) amino butanoic acid (7a)4-(4-acetamidophenyl)-3-hydroxy -2-((methoxy carb onyl) amino)-4-oxobutanoic acid (7b) 4-(4-aceta midophenyl)-3-hydroxy-4-oxo-2-(((vinyloxy)carbonyl)amino) butanoic acid (7c)

Equimolar amounts of epoxide (**2)** (0.03 mol) and BF_3etherate (0.03 mol) as catalyst were stirred in benzonitrile, acetonitrile, and acrylonitrile (10 cm^3) as a solvent and reagent was stirred at room temperature for 5h. The reaction

mixture was poured into aqueous $NaHCO_3$ (5 %) and extracted with ether. The solid obtained was crystallized from the proper solvent. IR spectra showed absorption bands at 3155—3440 cm^{-1} ((NH) and (OH)).

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