

Synthesis of Some New Heterocyclic Compounds from 3-Aroylprop-2-Enoic Acid

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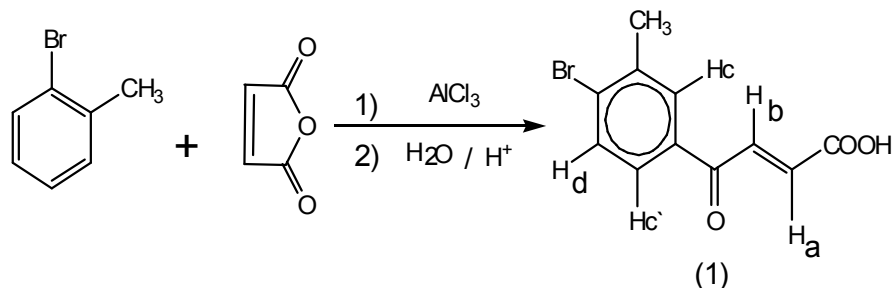
Abstract: The present work included the synthesis of 3-arylprop-2-enoic acid 1. When 1 was allowed to react with 4-hydroxyquinazoline (2) it gave the derivative of quinazoline 3, which in turns was allowed to react with hydroxylamine hydrochlorid in refluxing pyridine to give 6-oxazinone derivative (6). On the other hand, reaction of hydrazine hydrate with the adduct 3 in refluxing ethanol resulted in the pyridazinone derivative 7. The present work was extended to include studying of the behavior of starting compound 1 towards 6-chloro-2-methyl chromone (9).

Kye words: Aroylprop • Synthesis • Heterocyclic • Quinazoline

INTRODUCTION

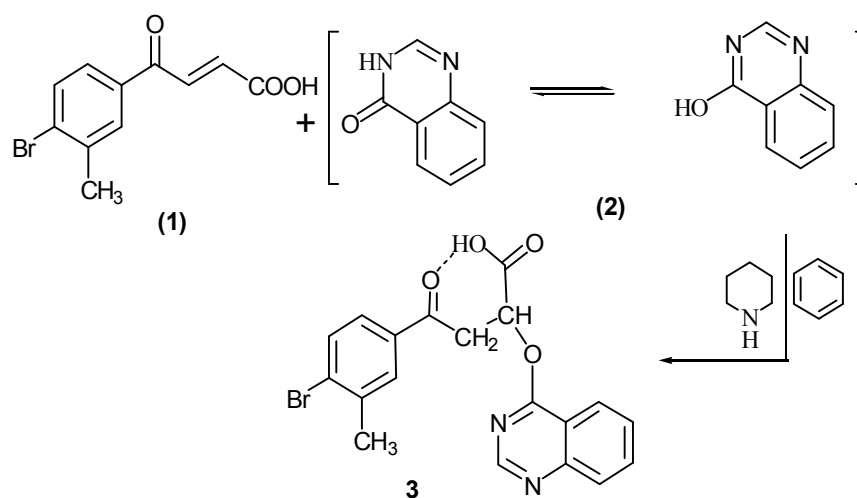
A large number of Aroylacrylic acids and it's derivatives were reported to exhibit biological activities [1,2], also a large number of pyridazine-3-one derivatives and some derivatives of oxazines was reported to exhibit insecticidal [3], allergenic [4], antihypertensive [5,6], analgesic [7,8], anti-inflammatory and bactericidal [9]activities. This inspired us to prepare some new compounds of classes mentioned from the starting material 3-(4-bromo-3-methylbenzoylprop-2-enoic acid) (1). This study was carried out to synthesis some new heterocyclic compounds which might have expected biological activities.

The starting compound 3-(4-Bromo-3-methyl) benzoylprop-2-enoic acid derivative 1 was synthesized as the reported method [3], by treating 2-Bromotoluene with maleic anhydride in the presence of anhydrous aluminum chloride as a catalyst.



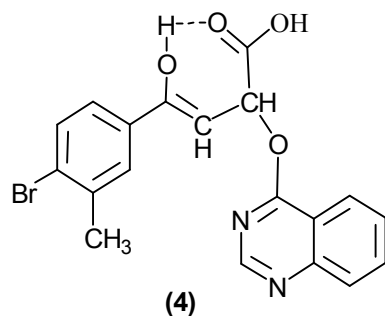
The structure of the compound 1 is established from its spectral data and rigidly confirmed by m.p. comparison with that reported [3].

Treatment of 3-aryl prop-2-enoic acid derivative 1 with benzo[d]pyrimidine derivative 2 in toluene and in the presence of catalytic amount of piperidine afforded 4-[(4-Bromo-3-methyl) benzoylmethyl]carboxylmethoxy benzo[d]pyrimidine (3).



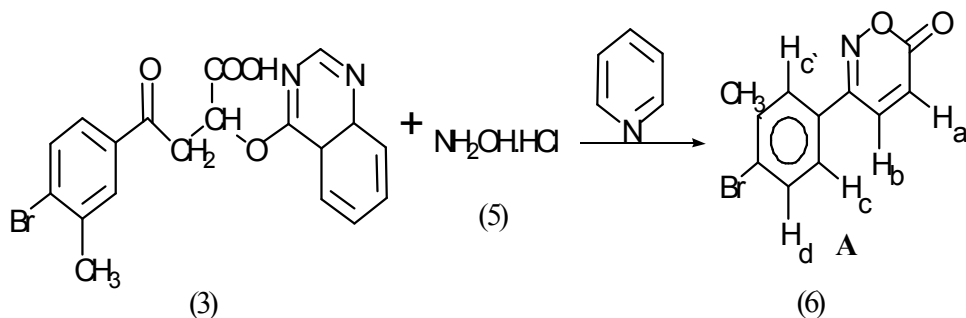
The structure of compound 3 confirmed by correct microanalytical data and also by spectral evidence. Thus its infrared spectrum exhibits bands corresponding to $\nu_{\text{OH(br)}}$ at 3344, 3228, 3184 cm^{-1} , $\nu_{\text{CH(aryl)}}$ at 3100 cm^{-1} , $\nu_{\text{CH(alkyl)}}$ at 2926, 2851 cm^{-1} , $\nu_{\text{C=O(acid)}}$ at 1711 cm^{-1} , $\nu_{\text{C=O(ketone)}}$ at 1658, $\nu_{\text{C=N}}$ and/or $\nu_{\text{C=C}}$ at 1627, 1580 as well as $\delta_{\text{4-H}}$ at 768 cm^{-1} .

Moreover, the $^1\text{H-NMR}$ spectrum of compound 3 which is devoid of any absorptions correlated with protons of $\text{CH}_2\text{-CH}$ -group, but exhibits from low to high field two exchangeable broad singlets and eight aromatic protons as well as two doublets corresponding to one olefinic and one methine protons suggests the existence of compound 3 in solution as its chelated tautomer 4 shown.



$^1\text{H-NMR}$ (DMSO) δ 2.44 (s, 3, CH_3), 4.22 (d, H_a , $J = 14.0$ Hz), 6.53 (d, H_b , $J = 15$ Hz), 8.02 (br.s, CH=OH exchangeable), 7.61-7.99 (m, 8, ArH), 11.03 (br.s, C=OH exchangeable).

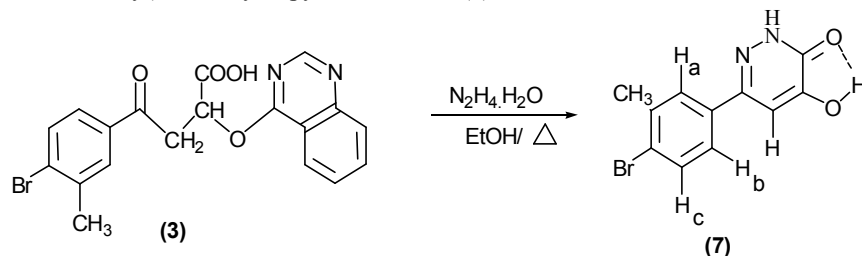
On the other hand reaction of benzo[d]pyrimidine derivative 3 with hydroxylamine hydrochloride in refluxing pyridine afforded the respective 3-(4-bromo-3-methyl)phenyl-6-oxo-6-hydro-1,2-oxazine(6).



The structure of compound 6 is substantiated spectroscopically and chemically. Thus, its infrared spectrum shows absorption bands corresponding to $\nu_{\text{CH(aryl)}}$ at 3070 cm^{-1} , $\nu_{\text{CH(alkyl)}}$ at $2999, 2928\text{ cm}^{-1}$, $\nu_{\text{C=O}}$ at 1765 cm^{-1} , $\nu_{\text{C=N}}$ and/or $\nu_{\text{C=C}}$ at $1628, 1534$. The higher value of absorption for the carbonyl group is a good evidence for the existence of the oxazinone ring system. Moreover the $^1\text{H-NMR}$ spectrum which is devoid of any signals corresponding to the aromatic protons of benzo pyrimidine ring, instead it revealed doublet signals correlated with the two olefinic protons H_a and H_b is in accord with the proposed structure. The appearance of extra doublet signals corresponding to the two olefinic protons, as well as the aromatic protons is due to their existence in two different magnetic environments, which suggests the presence of compound 6 as a mixture of two conformers 6A and 6B, respectively. $^1\text{H-NMR}$ (DMSO) δ 2.52 (s, 3, CH_3), 6.99, 7.12 (doublet, H_a , $J_{ab} = 10.16, 9.60\text{ Hz}$), 6.65, 7.72 (doublet, H_b , $J_o = 8.35\text{ Hz}$), 7.73-7.89 (two doublets doublets, H_c , $J_o = 8.34\text{ Hz}$, $J_m = 1.95\text{ Hz}$), 7.91, 7.95 (two doublets, H_c , $J_m = 2.1\text{ Hz}$), 7.98, 8.18 (doublet, H_b , $J_{ab} = 10.2, 10.4\text{ Hz}$).

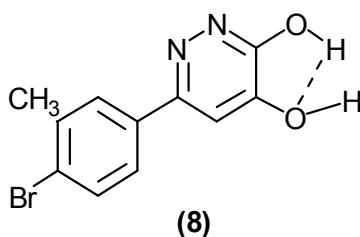
A chemical proof for the structure 6 was given by comparison with an authentic sample prepared by similar treatment of 1 with hydroxylamine, which gives a product identified as a compound 6 by m.p and m.m.p determination

When benzo [d] pyrimidine derivative 3 was allowed to react with hydrazine hydrate in refluxing ethanol, it afforded 4-hydroxy-6-(4-bromo-3-methyl)-2,3-dihydropyridazin-3-one (7).



The structure of 7 is deduced from microanalytical and spectral data. Thus Its infrared spectrum shows absorption characteristic for ν_{NH} at $3209, 3164$, $\nu_{\text{OH(br)}}$ in the region $2307-2800\text{ cm}^{-1}$, $\nu_{\text{CH(aryl)}}$ at 3017 cm^{-1} , $\nu_{\text{C=O(amide)}}$ at 1677 cm^{-1} , $\nu_{\text{C=N}}$ and/or $\nu_{\text{C=C}}$ at $1634, 1566, 1531\text{ cm}^{-1}$.

A good evidence for the assigned structure was given from its $^1\text{H-NMR}$ spectrum, where it is devoid of any signals corresponding to the amido proton in the down field region or the protons of the benzopyrimidine moiety, instead it shows exchangeable broad signals hidden in the region δ 3-4 correlated with the two (OH) groups, this suggests its existence in solution as its chelated tautomer 8 shown.



$^1\text{H-NMR}$ (DMSO) δ 2.29 (s, 3, CH_3), 3.44-3.56 (br.s, 2 OH hidden in the region of D_2O), 7.01 (s, 1, CH=), 7.32 (d, H_c , $J_o = 8.51\text{ Hz}$), 7.69 (dd, H_b , $J_o = 8.29\text{ Hz}$, $J_m = 2.31\text{ Hz}$), 8.00 H_a , $J_m = 2.32\text{ Hz}$

When prop-2-enoic acid derivative 1 was treated with 6-chloro-2-methylchromone (9) in presence of sodium ethoxide in ethanol, it gave 1-(4-bromo-3-methyl) phenyl-3-carboxy-8-chlorobenzo [b] chromone (10)

The structure of compound 10, is evidenced from microanalytical and spectral data, Its infrared spectrum reveals absorption bands corresponding to $\nu_{\text{OH(br.) (acid)}}$ at 3301 cm^{-1} , $\nu_{\text{CH(aryl)}}$ at 3074 cm^{-1} , $\nu_{\text{CH(alkyl)}}$ at $2960, 2944, 2872\text{ cm}^{-1}$, $\nu_{\text{C=O}}$ (sh.) (γ -pyrone) at 1747 cm^{-1} , $\nu_{\text{C=O(acid)}}$ at 1699 cm^{-1} , $\nu_{\text{C=C}}$ at $1661, 1600\text{ cm}^{-1}$. A further support for the structure of compound 10 is gained from $^1\text{H-NMR}$ spectroscopy as the spectrum exhibits exchangeable OH, methyl proton as well as aromatic protons.

$^1\text{H-NMR}$ (DMSO) δ 2.44 (s, 3, CH_3), 7.61-8.12 (m, 8, ArH), 13.41 (br.s, OH exchangeable).

The reaction seems to proceed via Michael addition of a carbanion formed from (9) to the unsaturated carbon, β -to the aroyl group of compound 1 followed by cyclization and then dehydrogenation [3].

Experimental

All melting points are uncorrected. The infrared spectra are recorded on FTIR Mattson (infinity series) spectrometers as KBr discs. The $^1\text{H-NMR}$ spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS. TLC was runned using TLC aluminium sheets silica gel F₂₅₄ (Merck).

Starting Material

General Procedure: Anhydrous aluminium chloride (130 mmole) was added portionwise to a stirred solution of maleic anhydride (85 mmole) in o-bromotoluene (85 mmole) in an ice bath. The whole mixture was stirred at room temperature for further 6 hrs. then left to stand overnight. The precipitated solid material which formed after addition of ice cold hydrochloric acid (25 ml) was filtered off, dried and the crude product was recrystallized from benzene to give E,E-3-(4-bromo-3-methyl)benzoyl-prop-2-enoic acids (1A,B) (75% yield) yellow crystals, m.p. 131-133°C. Lit.⁽¹⁰⁾, m.p. 136-139°C. Anal calcd for C₁₁H₉O₃Br: C, 49.10; H, 3.37; Br, 29.69. Found: C, 49.11; H, 3.42;

Reaction of 1 with 4-hydroxybenzo[d]pyrimidine (2): A mixture of 1 (4 mmole), 2 (4 mmole) and few drops of piperidine was refluxed in benzene (25 ml) for 4 hrs. The reaction mixture was left to stand at room temperature for 4 days. The precipitated solid was filtered off and then recrystallized from methanol to give 4-[(4-bromo-3-methyl)benzoylmethyl] carboxymethoxybenzo-[e] pyrimidine (3), (64% yield), pale yellow crystals, m.p. 166-169°C. Anal. Calcd for C₁₉H₁₅N₂O₄Br: C, 54.96; H, 3.64; N, 6.75; Br, 19.24. Found: C, 54.71; H, 3.54; N, 6.79;

Reaction of 3 with Hydroxylamine Hydrochloride in Pyridine: A solution of 3 (2 mmole) in pyridine (10 ml) was refluxed with hydroxylamine hydrochloride (2 mmole) for 3 hrs. The reaction mixture was left to cool, then poured into cold water. The precipitated solid was filtered off and recrystallized from benzene/ethanol mixture to give 3-(4-bromo-3-methyl)phenyl-6-oxo-6-hydro-1,2-oxazine (6), (41% yield), white crystals, m.p. 120-124°C. Anal. Calcd for C₁₁H₈NO₂Br: C, 49.65; H, 3.03; N, 5.26; Br, 30.03. Found: C, 49.73; H, 3.11; N, 5.33

Reaction of 3 with Hydrazine Hydrate: Hydrazine hydrate (1 ml) was refluxed for 3 hrs. with 3 (4 mmole) in ethanol (15 ml). The reaction mixture was concentrated and left to stand at room temperature. The precipitated solid was filtered off, then recrystallized from ethanol to give 4-hydroxy-6-(4-bromo-3-methyl) phenyl-2,3-dihydropyridazin-3-one (7), (66% yield), white crystals, m.p. 232-234°C. Anal. Calcd for C₁₁H₉N₂O₂Br: C, 47.00; H, 3.23; N, 9.97. Br, 28.42 Found: C, 47.12; H, 3.19; N, 9.79.

Reaction of 1 with 6-chloro-2-methylchromone (9): The chromone derivative 9 (3 mmole) and the acid 1 (3 mmole) were added successively to a stirred solution of sodium ethoxide (3 mmole) in absolute ethanol (15 ml). The reaction mixture then heated at 100°C under reflux for 6 hrs., then concentrated, cooled and poured into ice cold HCl. The precipitated solid was filtered off and crystallized with methanol to give the product 10.

1-[4-Bromo-3-methyl]phenyl-3-carboxy-8-chlorobenzo-[b]chromone (10), (12% yield), white crystals, m.p. 254-256°C. Anal. Calcd for C₂₁H₁₂O₄BrCl: C, 56.85; H, 2.73; Br, 18.01; Cl, 7.99 Found: C, 56.77; H, 2.69.

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