Synthesis and Characterization New Schiff Bases, Pyrazole and Pyrazoline Compounds Derived From Acid Hydrazide Containing Isoxazoline Ring

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Received in: 15 June 2014, Accepted in: 29 September 2014

Abstract
The work involves synthesis of new Schiff bases (V) a, b and (VI) a, b, pyrazoles (VII) a, b and pyrazolines (VIII) a, b derivatives containing isoxazoline unit starting with chalcones. 4-bromoacetophenone was reacted with 4-hydroxybenzaldehyde or 4-hydroxyacetophenone was reacted with 4-bromobenzaldehyde in basic medium to give chalcone by Claisen-Schmidt reaction. The chalcones [I] a, b was reacted with hydroxylamine hydrochloride to form isoxazolines [II] a, b, which were reacted with ethyl chloroacetate in basic medium to get ester compounds [III] a, b. The condensation new ester [III] a, b with hydrazine hydrate 80% yielded acid hydrazide [IV] a, b. The later compound refluxing with 4-substituted benzaldehyde in dry benzene to give Schiff bases (V) a, b and (VI) a, b while the reaction of acid hydrazide [IV] a, b with acetylacetone or ethyl acetocacetate to get pyrazoles (VII) a, b, pyrazolones (VIII) a, b respectively. The synthesized compounds were characterized by melting points, FTIR, mass and 1H NMR spectroscopy (of some of them).

Key Words: chalcones, Schiff bases, isoxazoline, pyrazole, pyrazoline.
Introduction

Chalcones were prepared by condensation of acetophenone with aromatic aldehydes in presence of basic medium [1]. The Chalcone derivatives are important intermediate and also act as precursor for the synthesis of novel cyanopyridines, pyrazolines, isoxazoles,pyrimidines and tetrazole [2]. Five-member heterocyclic compounds isoxazoline are important for pharmaceutical industry and material science due to their various applications. Isoxazoline are present in the structures of many natural products. In fact, isoxazoline have a broad spectrum of their biological and pharmacological activities [3-6].

Pyrazoles are one of the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Because of their aromaticity and wide application in pharmaceutical and material industry, they have gained significant interest among the scientist [7-10]. Also the pyrazoline showed a wide spectrum of biological activities such as anti-bacterial, antifungal, herbicidal and anti-choligenic [11-14]. In the view of the varied biological, pharmacological and industry applications, we have planned to synthesis some isoxazoline derivatives containing imine, pyrazole or pyrazoline unit.

Experimental

Chemicals

All chemicals were supplied by fluka, GCC, merck and sigma-Aldrich chemicals Co. and used as received.

Techniques

FTIR spectra were recorded using potassium bromide discs on a Shimadzu(Ir prestige - 21) ¹HNMR spectra were carried out by company:Bruker,model: ultra-shield 400MHz,origin: Switzerland and are reported in ppm(δ) DMSO were used as a solvent with TMS as an internal standard,measurements were made at Chemistry Department, science and Technology University, Jordan. The mass spectrum was recorded on shimadzu model 6CMS QL 1000 EX, made in Japan. Uncorrected melting points were determined by using Hot-Stage,Gallen Kamp melting point apparatus.

Synthesis

New compounds are synthesized according to scheme1
Synthesis of (chalcones) 3-(4-hydroxyphenyl)(4¯-bromophenyl)-2-propene-1-one[II]a and 3-(4¯-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one[II]b

Equimolar quantities of 4-bromo or 4-hydroxy acetophenone (0.01 mol),and 4-bromo or4- hydroxy benzaldehyde (0.01 mol) were dissolved in minimum amount of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture became cold. Then the mixture was poured slowly into 400 mL of ice water with constant stirring and kept in refrigerator for 24 hrs. The precipitate obtained was filtered [15],washed and recrystallized from ethanol .

Synthesis of 4-(3-(4`-bromophenyl)-4,5-dihydroisoxazol-5-yl)phenol [II]a and 4-(5-(4`-bromophenyl)-4,5-dihydroisoxazol-3-yl)phenol[II]b

A mixture of compound [II]a, b(0.01mol) ,ethyl α- chloro acetate (0.01 mol) and fused sodium acetate (0.03mol,2.46gm) in ethanol 25mL was refluxed for 4 hrs .Then cooled and
poured into cold water, the resulting soiled was filtered and from recrystallized ethanol [17] to give a new ester.

![Chemical structure](image)

**Scheme (1)**

**Synthesis of hydrazid derivatives [IV]_{a,b}**

A solution of ester [III]_{a,b} (0.06 mol) and hydrazine hydrate (15mL) in (25mL) of ethanol was heated to reflux during 4hrs. The mixture was then cooled to room temperature[18] and the solid obtained was filtered and recrystallized from ethanol. The physical properties of synthesized compounds [I]-[IV] were given in Table 1.

**Synthesis of Schiff base derivatives [V]_{a,b }, [VI]_{a,b}**

A mixture of new hydrazide [IV]_{a,b} (0.01 mol), different aromatic aldehyde (0.012 mol), dry benzene (10 mL) and 2 drops of glacial acetic acid was refluxed for 3hrs. The solvent was evaporated under vacuum and the residue crystallized from chloroform[19].

**Synthesis of pyrazole and pyrazoline derivatives [VII]_{a,b}, [VIII]_{a,b}**
A mixture of new hydriozide \([IV]_{a,b}\) (0.0028 mol) and \(\text{CH}_3\text{COCH}_2\text{COCH}_3\) or \(\text{CH}_3\text{COCH}_2\text{CO}_2\text{Et}\) (0.0028 mol) in abs. EtOH(20mL) was refluxed for 3hrs. the reaction mixture was cooled and the formed precipitate was filtered off and recrystallized to give new pyrazoles \([VII]_{a,b}\) or pyrazoline\([VIII]_{a,b}\), respectively. The physical properties of synthesized compounds \([V]-[VIII]\) were listed in Table 2.

**Results and Discussion**

The chalcones \([I]_{a,b}\) were synthesized by Claisen-Schemidt reaction from condensation aromatic aldehyde with acetophenone in NaOH. The compounds \([I]_{a,b}\) were characterized by melting points, FTIR spectroscopy. The FTIR spectra of compound\([I]_{a,b}\) showed appearance broad band \(\nu\) O-H between (3448-3250) cm\(^{-1}\), absorption sharp stretching band in the region (1681-1645) cm\(^{-1}\) due to C=O stretching with the appearance band between (1654-1610) cm\(^{-1}\) due to \(\nu\) C=C of chalcone unit and a stretching band at (680-675) cm\(^{-1}\) due to C-Br. Also the spectra showed disappearance characteristic bands of starting materials.

The isoxazoline compound \([II]_{a,b}\) was synthesized by the reaction of compound\([I]_{a,b}\) with hydroxylamine hydrochloride in basic medium. The FTIR spectra of compound \([II]_{a}\) showed disappearance the bands of C=O and C=C for chalcone moiety with the appearance of new bands for \(\nu\) C-Haliph. in the region (2920-2854) cm\(^{-1}\) and appearance of a stretching band at (1643-1640) cm\(^{-1}\) due to \(\nu\) C=N of isoxazoline ring (endo cyclic) and \(\nu\) C-O of isoxazoline ring between (1095-1070) cm\(^{-1}\).

The ester compounds \([III]_{a,b}\) were synthesized by the reaction of compounds \([II]_{a,b}\) with ethylα-chloro acetate in fused sodium acetate. The FTIR spectra of compounds \([III]_{a,b}\) showed a significant band at 1735cm\(^{-1}\) which could be attributed to stretching vibration of the carbonyl of ester group, together with disappearance absorption band due to \(\nu\) O-H group for compound\([III]_{a,b}\). The\(^1\)HNMR spectrum of ester compound \([III]_{a}\) (in DMSO as a solvent), Figure(1) showed the following characteristics chemical shifts: a singlet signal at \(\delta\) 4.25 ppm for two protons of OCH\(_2\) group while the aquaterale signal of protons of CH\(_2\) group appear at \(\delta\) (3.12-3.20) ppm, and a triplet signal at \(\delta\) 1.79 ppm due to three protons of CH\(_3\) group. Also the spectrum showed many signals in the region \(\delta\) (6.79-8.04) ppm could be attributed to eight aromatic protons, a triplet signal at \(\delta\) (3.95-4.05) ppm and doublet of doublet at \(\delta\) (2.95-3.02) ppm were assigned to one proton at C-5 and two protons at C-4, respectively of isoxazoline ring.

The condensation of ester with hydrazine hydrate to get new acid hydrazides\([IV]_{a,b}\). The FTIR spectra of compounds\([IV]_{a,b}\) showed a shift in the carbonyl stretching band to ester group of compound\([III]_{a,b}\) to 1645cm\(^{-1}\) for amide group of hydrazide\([IV]_{a,b}\) also showed three bands in the range (3334-3115) cm\(^{-1}\) which is assigned to asymmetric and symmetric bands of NH\(_2\) and NH groups. The\(^1\)HNMR spectrum of acid hydrazide\([IV]_{b}\) (in DMSO as a solvent), Figure(2) exhibited a sharp singlet at \(\delta\) 4.21 ppm for two proton of OCH\(_2\) group, two signals at \(\delta\) 3.83 ppm and \(\delta\) 4.46 ppm due to two protons at C-4 and one proton at C-5, respectively of isoxazoline ring. A broad signal at \(\delta\) 3.4 ppm could be assigned for two protons of NH\(_2\) group and another broad signal at \(\delta\) 11.3 ppm due to proton of NH group. Finally many signals between \(\delta\) (6.63-7.87) ppm for eight aromatic protons.

The new Schiff bases compound \([V]_{a,b}\) and\([VI]_{a,b}\) were synthesized by the refluxing of compound \([IV]_{a,b}\) with different aromatic aldehydes in benzene. The compounds were characterized by melting points, FTIR spectroscopy. The characteristic FTIR absorption bands of compounds \([V]_{a,b}\) and\([VI]_{a,b}\) as Figure(3) showed the disappearance of two absorption bands due to NH\(_2\) stretching of acid hydrazide together with the appearance of a
stretching bands at (1682-1671) cm\(^{-1}\) assignable to \(\nu\) C=N. The characteristics FTIR absorption bands of new Schiff bases [V]\(_a\), \(_b\) and [VI]\(_a\), \(_b\) were listed in Table 3. The refluxing hydrazide [IV] with acetyl acetone led to form new pyrazoles [VII]\(_a\), \(_b\) . These compounds were characterized by melting points and FTIR spectroscopy. The FTIR spectra as Figure(4) showed the disappearance of three absorption bands due to NH\(_2\) and NH groups together with the appearance of the stretching bands near (1645) cm\(^{-1}\) assignable to \(\nu\) C=N group and 1371 cm\(^{-1}\) due to N-N for pyrazole ring. Also pyrazoline [VIII]\(_a\), \(_b\) is produced from the reaction hydrazide with Ethyl aceto acetate. This compound is identified by melting points, FTIR spectra and mass spectroscopy. The FTIR spectra as Figure(5) showed the disappearance of three absorption bands due to NH\(_2\) and NH groups together with the appearance of the stretching band around 1650 cm\(^{-1}\) due to \(\nu\) C=N band and new absorption band at (1735-1729) cm\(^{-1}\) due to C=O (endo cyclic).

The mass spectrum of compound [VIII]\(_a\) Figure(6) showed the most fragments in scheme 2.

Scheme (2)
References

Table No. (1) The physical properties of Chalcones [I]a, b and compounds [II]a, b-[IV]a, b

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Nomenclature</th>
<th>Structural formula</th>
<th>Molecular formula</th>
<th>M. P 0°C</th>
<th>Yield %</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>[I]a</td>
<td>3-(4’-hydroxyphenyl)(4’-bromophenyl)-2-propene-1-one</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>C15H11O2Br</td>
<td>158-160</td>
<td>45</td>
<td>Yellow</td>
</tr>
<tr>
<td>[I]b</td>
<td>3-(4’-bromophenyl)-1-(4’-hydroxyphenyl)-2-propen-1-one</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>C15H11O2Br</td>
<td>178-180</td>
<td>90</td>
<td>White</td>
</tr>
<tr>
<td>[II]a</td>
<td>3-[4’-bromophenyl]-5-(4’-hydroxyphenyl)-4,5-dihydroisoxazole</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>C15H12NO2Br</td>
<td>68-70</td>
<td>42</td>
<td>Yellow</td>
</tr>
<tr>
<td>[II]b</td>
<td>3-[4’-hydroxyphenyl]-5-(4’-bromophenyl)-4,5-dihydroisoxazole</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>C15H12NO2Br</td>
<td>130-132</td>
<td>60</td>
<td>Off white</td>
</tr>
<tr>
<td>[III]a</td>
<td>Ethyl 2-{4-[3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]phenoxy}acetate</td>
<td><img src="structure5.png" alt="Structure" /></td>
<td>C10H16NO4Br</td>
<td>100-102</td>
<td>59</td>
<td>Yellow</td>
</tr>
<tr>
<td>[III]b</td>
<td>Ethyl 2-{4-[5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl]phenoxy}acetate</td>
<td><img src="structure6.png" alt="Structure" /></td>
<td>C10H18NO4Br</td>
<td>155-158</td>
<td>70</td>
<td>Off white</td>
</tr>
<tr>
<td>[IV]a</td>
<td>2-{4-[3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]phenoxy}acetohydrazide</td>
<td><img src="structure7.png" alt="Structure" /></td>
<td>C17H16N2O3Br</td>
<td>85-88</td>
<td>61</td>
<td>Pale green</td>
</tr>
<tr>
<td>[IV]b</td>
<td>2-{4-[5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl]phenoxy}acetohydrazide</td>
<td><img src="structure8.png" alt="Structure" /></td>
<td>C17H16N2O3Br</td>
<td>120-122</td>
<td>65</td>
<td>Pale green</td>
</tr>
</tbody>
</table>
### Table No.(2) The physical properties of compounds [V]a,b-[VIII]a,b

<table>
<thead>
<tr>
<th>Com. No.</th>
<th>Nomenclature</th>
<th>Structural formula</th>
<th>Molecular formula</th>
<th>M. P °C</th>
<th>Yield %</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>[V]a</td>
<td>{4-[3-(4-bromophenyl)-4,5-dihydro-isoxazol-5-yl]phenoxy}(4’-nitrobenzylidene)acetic hydrazide.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{24}H_{19}N_{4}O_{5}Br</td>
<td>288-290</td>
<td>82</td>
<td>Brown</td>
</tr>
<tr>
<td>[V]b</td>
<td>{4-[5-(4-bromophenyl)-4,5-dihydro-isoxazol-3-yl]phenoxy}(4’-nitrobenzylidene)acetic hydrazide.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{24}H_{19}N_{4}O_{5}Br</td>
<td>276-279</td>
<td>46</td>
<td>Yellow</td>
</tr>
<tr>
<td>[VI]a</td>
<td>{4-[3-(4-bromophenyl)-4,5-dihydro-isoxazol-5-yl]phenoxy}(4’-bromobenzylidene)acetic hydrazide.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{24}H_{19}N_{3}O_{3}Br_{2}</td>
<td>158-160</td>
<td>82</td>
<td>Brown</td>
</tr>
<tr>
<td>[VI]b</td>
<td>{4-[5-(4-bromophenyl)-4,5-dihydro-isoxazol-3-yl]phenoxy}(4’-bromobenzylidene)acetic hydrazide.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{24}H_{19}N_{3}O_{3}Br_{2}</td>
<td>110-114</td>
<td>92</td>
<td>Pale Brown</td>
</tr>
<tr>
<td>[VII]a</td>
<td>2-{4-[3-(4-bromophenyl)-4,5-dihydro-isoxazol-5-yl]phenoxy}-1-(3,5dimethyl-pyrazol -1-yl)ethanone.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{22}H_{20}N_{3}O_{3}Br</td>
<td>190-192</td>
<td>43</td>
<td>Brown</td>
</tr>
<tr>
<td>[VII]b</td>
<td>2-{4-[5-(4-bromophenyl)-4,5-dihydro-isoxazol-3-yl]phenoxy}-1-(3,5dimethyl-pyrazol -1-yl)ethanone.</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{22}H_{20}N_{3}O_{3}Br</td>
<td>100-103</td>
<td>89</td>
<td>Brown</td>
</tr>
<tr>
<td>[VIII]a</td>
<td>2(2-{4-[3-(4-bromo phenyl)-4,5-dihydro-isoxazol-5-yl]phenoxy}-acetyl)-5-methyl -pyrazolin-3-one</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{21}H_{18}N_{3}O_{4}Br</td>
<td>60-62</td>
<td>67</td>
<td>Brown</td>
</tr>
<tr>
<td>[VIII]b</td>
<td>2(2-{4-[5-(4-bromo phenyl)-4,5-dihydro-isoxazol-3-yl]phenoxy}-acetyl)-5-methyl -pyrazolin-3-one</td>
<td><img src="image" alt="Structural formula" /></td>
<td>C_{21}H_{18}N_{3}O_{4}Br</td>
<td>107-109</td>
<td>83</td>
<td>Brown</td>
</tr>
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</table>
Table No.(3): Characteristic FTIR absorption band of compounds [Ⅴ]a, b - [Ⅷ]a, b

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Characteristic bands FTIR spectra(cm⁻¹)</th>
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<tr>
<td></td>
<td>vNH</td>
</tr>
<tr>
<td>[Ⅴ]a</td>
<td>3271</td>
</tr>
<tr>
<td>[Ⅴ]b</td>
<td>3245</td>
</tr>
<tr>
<td>[Ⅵ]a</td>
<td>3259</td>
</tr>
<tr>
<td>[Ⅵ]b</td>
<td>3248</td>
</tr>
<tr>
<td>[Ⅶ]a</td>
<td>3066</td>
</tr>
<tr>
<td>[Ⅶ]b</td>
<td>3077</td>
</tr>
<tr>
<td>[Ⅷ]a</td>
<td>3066</td>
</tr>
<tr>
<td>[Ⅷ]b</td>
<td>3077</td>
</tr>
</tbody>
</table>

Figure No.(1): 1HNMR-Spectrum of compound
Figure No. (2) : 1HNMR-Spectrum of compound [IV]b

Figure No. (3): FTIR-Spectrum of compound [V]b
Figure No. (4): FTIR-Spectrum of compound [VII]a

Figure No. (5): FTIR-Spectrum of compound [VIII]b
Figure No. (6): Mass - spectrum of compound [VIII]a
تحضير و تشخيص مركبات قواعد شف و بايارازول و بايارازولين جديدة مشتقة من حامض الهيدرازид الحاوي على حلقة الأيزوكزولين.

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استلم البحث: 15 حزيران 2014، قيل البحث في: 29 ايلول 2014

الخلاصة

يتضمن هذا البحث تحضير وتحضير مشتقات جديدة لقواعد شف وبايارازول وبايارازولين وبايارازولين تحتوي على وحدات الأيزوكزولين باستعمال الجالكون مادة أساسية يحضر الجالكون من فعالة 4-برومو أسيتوفينون مع 4- هيدروكسي بنزاليدي أسلوب النقل 4- هيدروكسي أسيتوفينون مع 4- برومو بنزالدي هيدروكسي في وسط قاعدي يتفاعل كليتين شمطت. يتفاعل الحالكون مع هيدروكسي أسيتوفنون ليعطي الأيزوكزولين مع هيدروكسي أسيتوفنون الحالكون الذي متى تفاعلته مع أثيل كلورو أسيتيل في وسط قاعدي لنتج الصرف على مركب أستري b I وحية تكسير الأستر الناتج مع الهيدرازيد النتيجة على حامض الهيدرازيد الذي يصم عكساً مع البنزالدي هيدروكسي الألياف ليعطي قواعد [IV]a
[VI]a, b
[v]a, b
[III]a, b
[II]a, b
[III]a, b
الكلمات المفتاحية: الجالكون, قواعد شف, الأيزوكزولين, البيبارازول, البيبارازولين