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Synthesis of some new 4-(2,4-dimethyl-phenyl)-2*H*-phthalazinone derivatives

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Abstract

Aroylation of *m*-xylene by phthalic anhydride under Friedel craft's reaction conditions to afford the corresponding *o*-aroylbenzoic acid derivative (2), which followed by cyclization reaction with hydroxylamine hydrochloride to produce the correlating benzoxazinone derivative (3), which was utilized as a precursor for the formation of some novel phthalazinone derivatives (4-6). This transformation was achieved by interactions with thiosemicarbazide, thiocarbohydrazide, and hydrazine monohydrate and/or ammonium acetate under suitable conditions. 4-Substituted-1(2*H*)- phthalazinone derivative (6), which undergoes *N*-alkylation using ethyl bromoacetate to produce the phthalazinone acetic acid ethyl ester derivative (7), that followed by the interaction with hydrazine monohydrate to afford the phthalazinone acetic acid hydrazide derivative (8). The latter product was conducted with different aromatic acid compounds in presence of $POCl_3$, to give the correlating oxadiazoles (9,10). The chemical structures of all the synthesized compounds are confirmed using physical and spectral data analyses like FT- IR, ^{1}H-NMR, and mass spectroscopy.

Keywords: benzoxazinone**,** 1,2,4-triazolo-phthalazine, 1,2,4,5-tetrazino-phthalazine, 1(2*H*)-phthalazinone, 1,3,4-oxadiazol-phthalazinone.

1. Introduction

Due to their large applicability, phthalazinones are the subject of strong interest in recent decades in the preparation of heterocycles [1]. In nature, heterocyclic compounds with nitrogen atoms exist very commonly and are vital for life. Examples of such compounds are phthalazinone derivatives.

Moreover, phthalazinones are used in the production of many highly relevant compounds, such as platelet aggregation inhibitors [2], poly (ADP ribose) polymerase inhibitors [3], phosphodiesterase inhibitors [4]. According to the higher stability of 4-(2,4-dimethyl phenyl)-1(2*H*)-phthalazinone, it is used as a building block in the synthesis of highly functionalized new phthalazinones that could have potent application in biological and medicinal terms.

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2. Experimental

All the reported melting points are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam SP1025 spectrophotometer. ^{1}H-NMR spectra were carried on a Bruker at 400MHz using tetramethylsilane (TMS) as standard. EIMS were performed at 70eV with Shimadzu GCMS (QP1000 EX).

2.1. Synthesis of 2-(2,4-Dimethylbenzoyl)-benzoic acid (2)

In a three-necked flask fitted to the condenser, a mixture of phthalic anhydride (14.8 g, 0.1 mol) and m-xylene (15 mL) was placed on an ice bath, followed by addition of anhydrous aluminum trichloride (20 g, 0.15 mol) with small ratios, with a good stirring for 30 mins. After addition was finished, the reaction mixture was refluxed for 3h, the mixture permitted to sit out at room temperature overnight. Diluted HCl-ice added to the mixture and the surplus of m-xylene was removed by using steam distillation procedure. The separated solid was filtrated off, washed with water and dried. The crude product was recrystallized from 50% ethanol to give (2) (17.1 g, 68% yield) as colorless crystals; Mp 118-120°C; IR (KBr) *v (cm^{-1})*: 1689, 1709 correlating to 2 C=O (ketonic and acidic groups, respectively) and 3467, 2545 corresponding to (OH) of carboxylic group.

2.2. Synthesis of 4-(2,4-Dimethylphenyl)-1H-benzo[d] [1,2] oxazin-1-one (3)

A mixture of 2.54 g (2) (0.01 mol) and 0.7 g of hydroxylamine hydrochloride (0.01 mol) in 30 mL dry pyridine. The reaction mixture was refluxed for 12h, cooling and acidification by HCl. The obtained solid was filtered off and recrystallized from ethanol to produce (3) (1.4 g, 56% yield) as colorless crystals; Mp 88–90 ^{o}C; ^{1}H-NMR(DMSO-d6) δ: 2.40 (s, 3H, CH3), 3.34 (s, 3H, CH3), 7.16–8.37 (m, 7H, Ar–H); IR (KBr) *v (cm^{-1})*: 1685 for (C=O), 1601 for (C=N); MS (70 eV) m/z (%): 251 (52, M^+) in accordance to its molecular formula $C_{16}H_{13}NO_2$.

2.3. Synthesis of 6-(2,4-Dimethylphenyl)- [1,2,4] triazolo[5,1-a] phthalazine-2(3H)-thione (4)

A mixture of 2.51 g (3) (0.01 mol) and 0.92 g of thiosemicarbazide (0.01 mol) in 30 mL dry pyridine. The reaction mixture was refluxed for 18h, cooling and acidification by HCl. The obtained solid was filtered off and recrystallized from ethanol to produce (4) (2.14 g, 66% yield) as colorless crystals; Mp 170–171 ^{o}C; ^{1}H-NMR(DMSO-d6) δ: 2.40 (s, 3H, CH3), 3.34 (s, 3H, CH3), 7.36–8.27 (m, 7H, Ar–H), 11.40 (s, 1H, NH, exchangeable with D_2O); IR (KBr) *v (cm^{-1})*: 3289, 3255 for (NH),

1284 for (C=S); MS (70 eV) m/z (%): 306 (1.56, M^+) in accordance to its molecular formula $C_{17}H_{14}N_4S$.

2.4. Synthesis of 7-(2,4-Dimethylphenyl)-2H- [1,2,4,5] tetrazino[6,1-a] phthalazine-3(4H)-thione (5)

A mixture of 2.51 g (3) (0.01 mol) and 1.06 g of thiocarbohydrazide (0.01 mol) in 30 mL dry pyridine. The reaction mixture was refluxed for 18h, cooling and acidification by HCl. The separated solid was filtered off and recrystallized from ethanol to produce (5) (2.06 g, 64% yield) as colorless crystals; Mp 160–161 ^oC; ^1H-NMR(DMSO-d6) δ: 2.40 (s, 3H, CH3), 3.34 (s, 3H, CH3), 7.16–8.37 (m, 7H, Ar–H), 10.40 (s, 1H, NH, exchangeable with D_2O), 11.30 (s, 1H, NH, exchangeable with D_2O); IR (KBr) *v* (cm^{-1}): 3274, 3178 for (2NH), 1288 for (C=S); MS (70 eV) m/z (%): 321 (22, M^+) in accordance to its molecular formula $C_{17}H_{15}N_5S$.

2.5. Synthesis of 4-(2,4-Dimethylphenyl)-2H-phthalazin-1-one (6)

Method 1. Hydrazine monohydrate (98%) 0.3 mL added to 2.54 g (2) (0.01 mol) in 15 mL ethanol absolute. The reaction mixture was refluxed for 6h, after cooling, poured into ice water. The obtained solid was filtered off and recrystallized from ethanol to produce (6) (1.8 g, 72% yield) as colorless crystals; Mp. 218–220 ^oC.

Method 2. A mixture of 2.51g of (3) (0.01 mol) and 0.77 g of ammonium acetate (0.1 mol) fused in oil bath around 180 ^oC for 2h, after cooling, the obtained solid was filtered off and recrystallized from ethanol to produce (6) (1.5 g, 60% yield) as colorless crystals; Mp 218-220 ^oC: ^1H-NMR(DMSO-d6) δ: 2.4 (s, 3H, CH3), 3.34 (s, 3H, CH3), 7.16–8.36 (m, 7H, Ar–H), 12.82 (s, 1H, NH, exchangeable with D_2O); IR (KBr) *v* (cm^{-1}): 3166 for (NH), 1677 for (C=O); MS (70 eV) m/z (%): 250 (99, M^+) in accordance to its molecular formula $C_{16}H_{14}N_2O$.

2.6. Synthesis of [4-(2,4-Dimethylphenyl)-1-oxo-1H-phthalazin-2-yl]-acetic acid ethyl ester (7)

A mixture of 2.5 g (6) (0.01mol), 5g ethyl bromoacetate (0.03mol) and 4.1 g K_2CO_3 (0.03mol) in 30 mL dry acetone, was refluxed for 30h, after cooling at room temperature, poured into cold water. The separated solid was filtered off and recrystallized from ethanol to produce (7) (2.4 g, 72% yield) as colorless crystals; Mp 149–150 ^oC; ^1H-NMR(DMSO-d6) δ:1.21(t, *J* =10 Hz, 3H, CH3CH2), 2.40 (s, 3H, CH3), 3.34 (s, 3H, CH3), 3.76 (q, *J* =10 Hz, 2H, CH2CH3), 4.98 (s, 2H, CH2CO), 7.16–8.37 (m, 7H, Ar–H); IR (KBr) *v* (cm^{-1}): 1754 for (C=O of ester), 1662 for (C=O

of cyclic amide); MS (70 eV) m/z (%): 336 (60, M^+) in accordance to its molecular formula $C_{20}H_{20}N_2O_3$.

2.7. Synthesis of [4-(2,4-Dimethylphenyl)-1-oxo-1H-phthalazin-2-yl]-acetic acid hydrazide (8)

A mixture of 3.36 g (7) (0.01 mol) and 2 mL hydrazine monohydrate in 50 mL ethanol absolute, the reaction mixture was refluxed for 6h, after cooling, poured into ice water. The separated solid was filtered off and recrystallized from ethanol to produce (8) (5 g, 88% yield) as white crystals; Mp 192–194 ^oC; ^1H-NMR(DMSO-d6) δ: 2.40 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.76 (s, 2H, NH_2 exchangeable with D2O), 4.27 (s, 2H, CH_2CO), 7.15–8.36 (m, 7H, Ar–H), 9.29 (s, 1H, NH exchangeable with D2O); IR (KBr) *v (cm^{-1})*: 3413 for (NH_2), 3166 for (NH), 1677 for (2 C=O of amide and cyclic amide); MS (70 eV) m/z (%): 322 (18, M^+) in accordance to its molecular formula $C_{18}H_{18}N_4O_2$.

2.8. Reaction of acetic acid hydrazide derivative 8 with different aromatic acids:

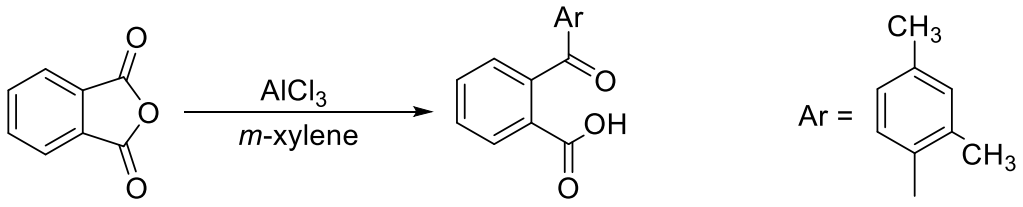
A mixture of 3.22g (8) (0.01mol), the appropriate aromatic acids; namely, 2-naphthyl acetic acid and 2-naphthoxyacetic acid (0.02 mol) in 10 mL $POCl_3$. The reaction mixture was refluxed in a water bath for 3h, then poured into 150 ml ice water. The obtained solid was filtered off and recrystallized from ethanol to give oxadiazoles (9) (3.54 g, 75% yield) and (10) (3.86 g, 79% yield).

2.8.1. Synthesis of 4-(2,4-Dimethylphenyl)-2-((5-(naphthalen-2-yl) methyl)-1,3,4-oxadiazol-2-yl) methyl) phthalazin-1(2H)-one (9): Mp 178–180 ^oC; ^1H-NMR(DMSO-d6) δ: 2.40, 3.13 (s, 6H, $2CH_3$), 3.92, 4.46 (s, 4H, $2CH_2$), 7.16–8.18 (m, 14H, Ar–H); IR (KBr) *v (cm^{-1})*: 1691 for (C=O of cyclic amide); MS (70 eV) m/z (%): 472 (6, M^+) in accordance to its molecular formula $C_{30}H_{24}N_4O_2$.

2.8.2. **Synthesis of 4-(2,4-Dimethylphenyl)-2-((5-((naphthalen-2-yloxy)methyl)-1,3,4-oxadiazol-2-yl) methyl) phthalazin-1(2H)-one (10):** Mp 116–124 ^oC; ^1H-NMR(DMSO-d6) δ: 2.41, 314 (s, 6H, $2CH_3$), 4.46 (s, 2H, CH_2), 5.49 (s, 2H, CH_2O), 7.21–8.13 (m, 14H, Ar–H); IR (KBr) *v (cm^{-1})*: 1661 for (C=O of cyclic amide); MS (70 eV) m/z (%): 488 (4, M^+) in accordance to its molecular formula $C_{30}H_{24}N_4O_3$.

3. Results and Discussion

Aroylation of *m*-xylene by phthalic anhydride under Friedel Craft's reaction conditions was achieved and 2-(2,4-Dimethylbenzoyl) benzoic acid (2) was obtained (Scheme 1).[5] The IR chart of compound (2) showed characteristic absorption bands at ν = 3467, 2545 and 1689, 1709 cm^{-1} correlating to OH of the carboxylic group, C=O of ketonic group and C=O of acidic group, respectively. *O*-aroylbenzoic acid derivative (2) was subsequently used as a starting point to build up the required heterocyclic compounds.

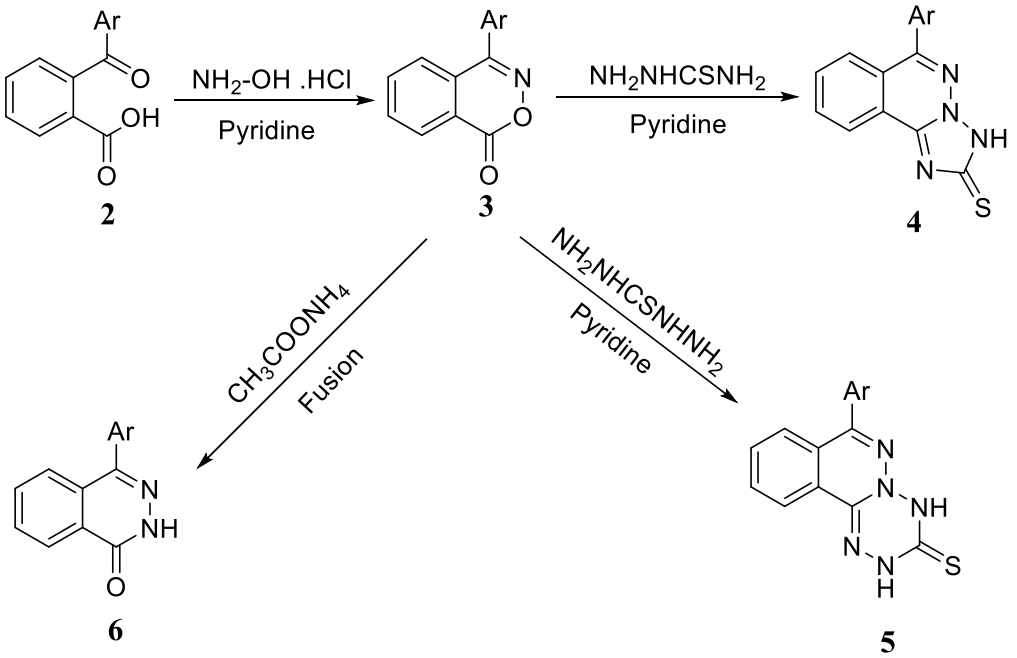


1 **2**

Scheme 1

Initially, cyclization of 2-(2,4-Dimethylbenzoyl) benzoic acid (2) with hydroxylamine hydrochloride in dry pyridine to afford 4-(2,4-dimethyl phenyl)-1*H*-benzo[d] [1,2] oxazin-1-one (3) (Scheme 2).[6] The structure of compound (3) was substantiated through its spectral data. The IR chart showed the disappearance of the hydroxy group of acid and the appearance of absorption bands at ν = 1685 cm^{-1} for C=O (of lactim ring) and 1601 cm^{-1} for C=N (of cyclic imine). Also, its mass spectrum displayed the predominant ion peak at *m/z* =251 (52%). phthalazine derivatives (4,5) were synthesized through the reactions of benzoxazinone derivative (3) with thiosemicarbazide or thiocarbohydrazide, respectively, in boiling dry pyridine (Scheme 2). The structure of compound (4) was confirmed by spectroscopic analysis. The IR chart exhibited strong absorption bands at ν = 3289 and 3255 cm^{-1} correlating to the NH group and was devoid of any absorption bands for the C=O of cyclic amide or NH_2 group. Further support was gained from its ^{1}H-NMR spectrum that showed NH signal at δ =11.40 ppm. In addition, its mass spectrum that displayed the predominant ion peak at *m/z* =306 (1.56%). The annulated phthalazine derivative (5) was confirmed from its spectral data. The IR chart was devoid of any absorption band for the C=O of cyclic amide group, but exhibited characteristic absorption bands at ν = 3274, 3178 cm^{-1} for 2NH groups, and an absorption band at ν =1288 cm^{-1} for C═S group, while ^{1}H-NMR

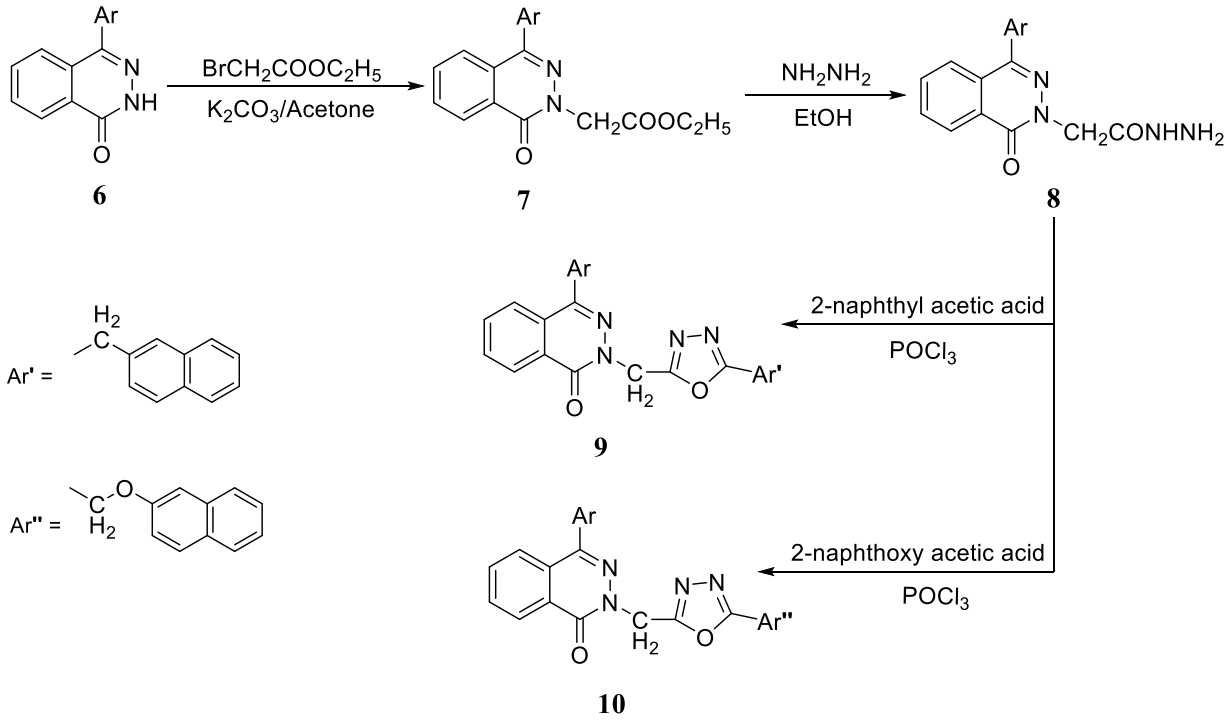
spectrum displayed signals at δ =10.40 and 11.30 ppm corresponding to 2NH groups exchangeable with D_2O. Condensation of *o*-aroylbenzoic acid (2) with hydrazine monohydrate in refluxing ethanol adopting the Y. A. El-Badry *et al* procedure [5] to afford the correlating phthalazinone derivative (6) (Scheme 2). Also, ammonolysis of benzoxazinone derivative (3) by fusion with ammonium acetate at 180 ^oC to afford the correlating phthalazinone derivative (6) which was assigned by its spectral data, in which the IR chart displayed the disappearance of the hydroxy group absorption bands and appearance of characteristic absorption bands at ν = 3166, 1677 cm^{-1} correlating to NH and C=O groups, respectively. In addition, the mass spectrum of (6) exhibited the molecular ion peak at *m/z* = 250 (99%), while ^{1}H-NMR spectrum displayed a characteristic signal at δ= 12.82 ppm for NH group.



Scheme 2

In our attempts to construct additional fused heterocycles, phthalazinone derivative (6) was allowed to react with ethyl bromoacetate (as a carbon nucleophile) and anhydrous K_2CO_3 in dry acetone to afford the correlating *N*-alkyl derivative (7) (Scheme 3). It is worthwhile to mention that no *O*-alkylation product was isolated and the reaction most probably took place *via* S_N^2 reaction mechanism and this may be attributed to the fact that the nitrogen atom is more nucleophilic than oxygen and therefore the *N*-alkylation product was the sole product.[6] The structure of compound (3) was substantiated through its spectral data, in which the IR chart showed absorption bands at ν = 1731, 1677 cm^{-1} correlating to the C=O group of the ester, and the C=O of

the cyclic amide group, respectively. In addition, the mass spectrum that displayed the predominant ion peak at *m/z* = 336 (60%), and ^{1}H NMR spectrum showed a triplet signal at δ= 1.21 ppm assigned for CH_3CH_2, a quartet signal at δ= 3.76 ppm assigned for CH_2CH_3 and a singlet signal at δ= 4.98 ppm assigned for CH_2CO. Also, compound (7) was confirmed chemically by the reaction with hydrazine monohydrate in boiling ethanol to afford [4-(2,4-Dimethylphenyl)-1-oxo-1*H*-phthalazin-2-yl]-acetic acid hydrazide (8).[7] The IR chart of compound (8) revealed characteristic absorption bands at ν = 3413, 3166 cm^{-1} for NH_2 and NH groups, respectively, and 1677 for C=O of both amide and cyclic amide groups. Also, the ^{1}H-NMR of (8) showed characteristic signals at δ= 4.76 ppm (s, 2H, NH_2 exchangeable with D_2O), δ= 4.27 ppm (s, 2H, CH_2CO), and δ= 9.29 ppm (s, 1H, NH exchangeable with D_2O). Motivated by the heightened functionality of the side chain of acetic acid hydrazide derivative (8), for instance, the reactions with different aromatic acids; namely, 2-naphthyl acetic acid and 2-naphthoxy acetic acid in $POCl_3$ to afford the correlating 1,3,4-oxadiazole derivatives (9,10), respectively, (Scheme 3).[8] The structures of compounds (9, 10) were substantiated through its spectral data, in which the IR chart showed the disappearance of the absorption bands of C=O of amide group and $NHNH_2$ of hydrazide group. In addition, the mass spectrum that displayed the predominant ion peak at *m/z* = 472 (6%) and 488 (4%), respectively. Finally, the ^{1}H NMR spectrum of compound (9) showed characteristic signals at δ= 3.92, 4.46 ppm correlating to $2CH_2$ groups, while compound (10) showed signals at δ= 4.46, 5.49 ppm correlating to CH_2 and CH_2O groups, respectively.



Scheme 3

4. Conclusion

The design and synthesis of benzoxazinone derivative (3), and 1(2*H*)-phthalazinone derivative (6) have been successfully reported here, and have been used as precursors for the construction of novel phthalazine and phthalazinone derivatives, such as the annulated 1,2,4-triazolo-phthalazine, 1,2,4,5-tetrazino-phthalazine, and 1,3,4-oxadiazol-phthalazinone.

5. References

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الملخص العربي

تحضير بعض مشتقات 4-(4,2-ثنائي ميثيل فينيل) -2*H*- فثالازين-1-اون الجديدة

ممدوح أحمد طه، إبراهيم عصام الدين الشامي، أسماء كمال مراد، أحمد ثابت على

قسم الكيمياء - كلية العلوم - جامعة الفيوم – الفيوم – مصر

الملخص العربي:

تم تحضير الأرويل بنزويك أسيد (2) عن طريق تفاعل الميتا إكسيلين مع الفيثاليك أنهيدرايد في وجود كلوريد الألومنيوم اللامائي يليها تفاعل الناتج مع الهيدروكسيل أمين هيدروكلوريد للحصول على مشتق البنزوكسيزينون (3) والذي من خلال تفاعله مع نيكليوفيلات نيتروجينية للحصول على مشتقات الفثالازينون (4-6). ثم تم دراسة سلوك مشتق الفثالازينون (6) تجاه الإلكترو فيل الكربوني (الإيثيل برومو أسيتات) والذي تم إثباته كيميائياً بالتفاعل مع الهيد رازين هيدرات للحصول على مشتق الحمض الهيرازيدي (8) والذي تم دراسة سلوكه تجاه الأحماض الأروماتية لتكوين مشتقات الأوكسادايازول (9,10). الشكل البنائي للمركبات التي تم تحضيرها تم إثباتها بتحليلات البيانات الفيزيائية والطيفية مثل الأشعة تحت الحمراء، البروتون النووي بالرنين المغناطيسي ومطياف الكتلة.