Synthesis of Some 1, 3, 4- Oxadizole Derivatives From Naproxen and Acetyl Chloride

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الخلاصة

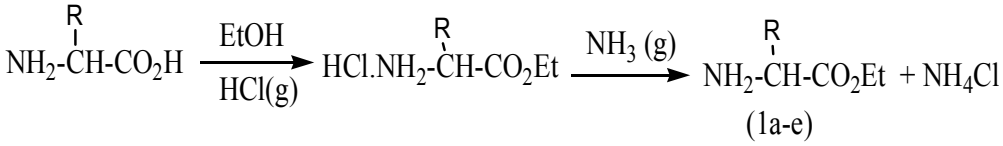
في هذا البحث تم تحضير عدد من المركبات 4,3,1- اوكسادايازول -2- ثايون من تفاعل النابروكسين (او استيل) هيدرازيدات الاحماض الامينية (كلايسين، فالين، ليوسين، ايزوليوسين، ثايروسين) مع ثنائي كبريتيد الكاربون في وسط قاعدي. كما تم تحضير عدد من مركبات 4,3,1- اوكسادايازول-2-اريل من تفاعل نابروكسين (او استيل) هيدرازيدات الاحماض الامينية مع بارا كلورو بنزالديهايد لاعطاء الهيدروزونات المقابلة ومن ثم حولقتها باستخدام ثنائي اوكسيد الرصاص. كما تم تحضير نابروكسين اميدات الاحماض الامينية من تفاعل الاسترات المقابلة مع غاز الامونيا تم اثبات تراكيب المركبات المحضرة بالطرق الفيزياوية والطيفية.

Abstract

A seriers of 1, 3, 4-oxadiazol-2-thion were synthesized by the reaction of naproxen (or acetyl) amino acid hydrazides (glycine, valine, leucine, isoleucine and tyrosine) with carbon disulphide in alkaline medium. The reaction of naproxen (or acetyl) amino acid hydrazides were treated with p-chloro benzaldehyde to give hydrazone, the hydrazones were then cyclized with lead dioxide to give 1, 3, 4-oxadiazol-2-aryl. Naproxen amino acid esters were treated with ammonia gas to give naproxen amino acid amids. The synthesized compounds were characterized by physical and spectral analysis.

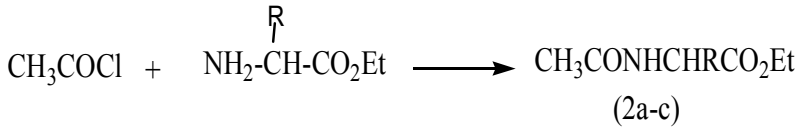
Introduction

In the family of heterocyclic compounds, nitrogen containing heterocycles with an oxygen atom are considered to be an important class of compounds in medicinal chemistry because of their interesting diversified biological application. The oxadiazole derivatives have been reported to have various biological activites including anti-microbal (1-3), anticancer (4, 5), anti inflammatory (6), anti-infective (7), and anti HIV (8). Substituted oxadiazole moiety has also been found to have other important activites such as antiviral (9), antifungal (10−12), antimycobacterial (13), anticouvulsant (14), antitumor (15), antimarlarial (16), and anti-hepatitis B viral activities (17). Substituted 1, 3, 4-oxadiazoles exhibit antibacterial (18-19), pesticidal (20) and analgesic activities (21−22). This paper describes the synthesis of new heterocyclic systems containing 1, 3, 4- oxadiazoles linked with naproxen.



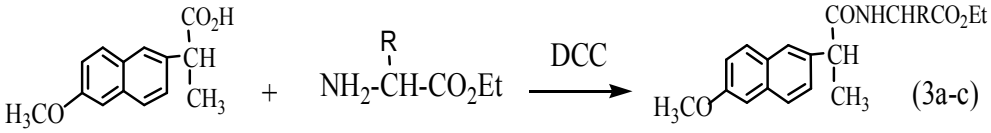
(1a-e)

R = -H , $-CH(CH_3)_3$, $-CHCH_2(CH_3)_2$, $-CH(CH_3)CH(CH_3)_3$, $-CHCH_2C_6H_4OH$



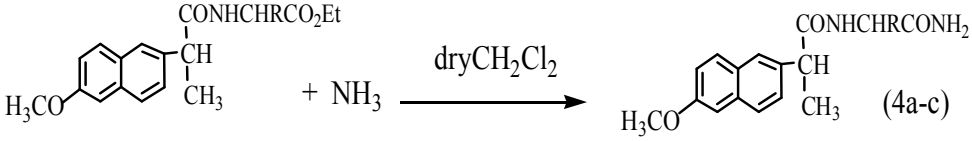
(2a-c)

R= $-CHCH_2(CH_3)_2$, $-CH(CH_3)CH(CH_3)_3$, $-CHCH_2C_6H_4OH$

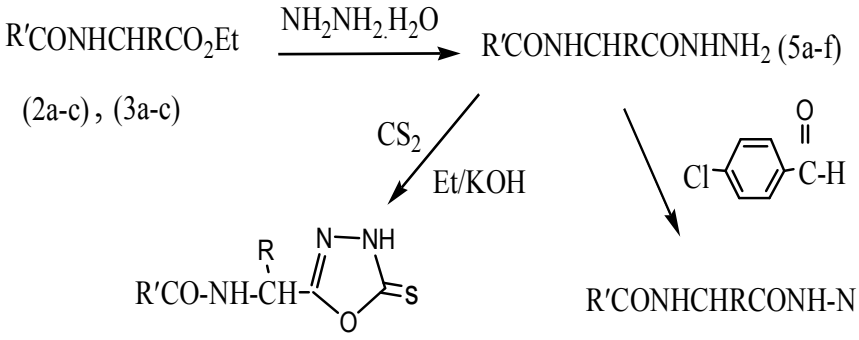


(3a-c)

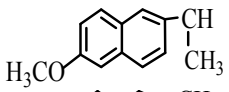
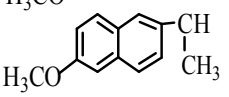
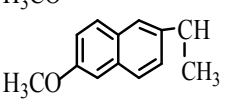
R= -H , $-CH(CH_3)_3$, $-CHCH_2(CH_3)_2$

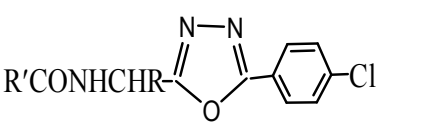


(3a-c) (4a-c)



(2a-c) , (3a-c) (5a-f) (6a-f) (7a-f)

5-8	R	R′
a	H	
b	$-CH(CH_3)_3$	
c	$-CHCH_2(CH_3)_2$	
d	$-CHCH_2(CH_3)_2$	CH_3
e	$-CH(CH_3)CH(CH_3)_3$	CH_3
f	$-CHCH_2C_6H_4OH$	CH_3



(8a-f)

Experimental

The melting points were measured on Bibby Scien Tific Limited, ST15 0SA, UK. IR spectra were recorded on FT-IR Spectrometer model Spectrum One, Perkin Elmer., using KBr discs. UV spectra were recorded on Lnicam, Disc PD2000-1, Mini Sipper Compot Tible. Amino acid esters (1a-e), acetyl amino acid esters (2a-c) and acetyl amino acid hydrazide (5d-f) were prepared using a previously reported method [23].

Synthesis of Naproxen Amino Acid Ester (3a-c)

To solution of 0.01M of Naproxen and 0.01M of amino acid ester in (50 ml) of dichloromethane is added 0.01M of N,N-dicyclo hexyl carbodiimide (DCC),The mixture is allowed to stirring over night at room temperature, The precipitated dicyclo hexyl urea is removed by filtration and the filtrate washed with water, diluted hydrochloric acid, water, half saturated sodium bicarbonate solution, water, and finally dried over anhydrous sodium sulfate, evaporation of the solvent gives residue mixture of crystals and oil. These are treated with a small amount of ether and filtrate; although the material is quite soluble in ether and hence is lost in appreciable amount when this solvent is employed, the white precipitate is recrystallized from chloroform. (Table 1)

Synthesis of Naproxen Amino Acid Amide (4a-c)

A stream of dry ammonia gas was passed through a solution of naproxen amino acid ester (0.01mole) in 50 ml of dichloro methane. The ammonium chloride was filtered off, the solvent was evaporated under reduced pressure, physical and spectral data are illustrated in (Table1).

Synthesis of Naproxen Amino Acid Hydrazide (5a-c)

A mixture of naproxen (or acetyl) amino acid ester (0.01 mole) and hydrazine hydrate (0.2 mole) in absolute ethanol (50 ml) was refluxed for 2 hrs. The mixture was cooled and the solid was filtered, dried and recrystallized from ethanol.

Synthesis of 1, 3, 4- Oxadiazole-2-Thione (6a-f)

To a mixture of (0.005 mole) naproxen (or acetyl) amino acid hydrazide (5a-f) in 50 ml of alcoholic potassium hydroxide solution (0.5%) was added slowly (12 ml) CS_2. After that the mixture was refluxed for 12 hours until the liberation of hydrogen sulfide was ceased (checked by moist paper with lead acetate). The solution was evaporated and the residual was poured on crushed ice, acidify with diluted HCl, filtered and dried.(Table 2).

Synthesis of Naproxen (or Acetyl) Amino Acid p-Chlorophenyl Hydrazones (7a-f)

P-chloro benzaldehyde (0.01 mole), naproxen (or acetyl) amino acid hydrazide (0.01 mole) in 50 ml of ethanol was refluxed for 2 hrs.

The solvent was condensed, and then the precipitate was filtered and recrystallized from benzene. (Table 2)

Synthesis of 1, 3, 4- Oxadiazole-2- Aryl (8a-f)

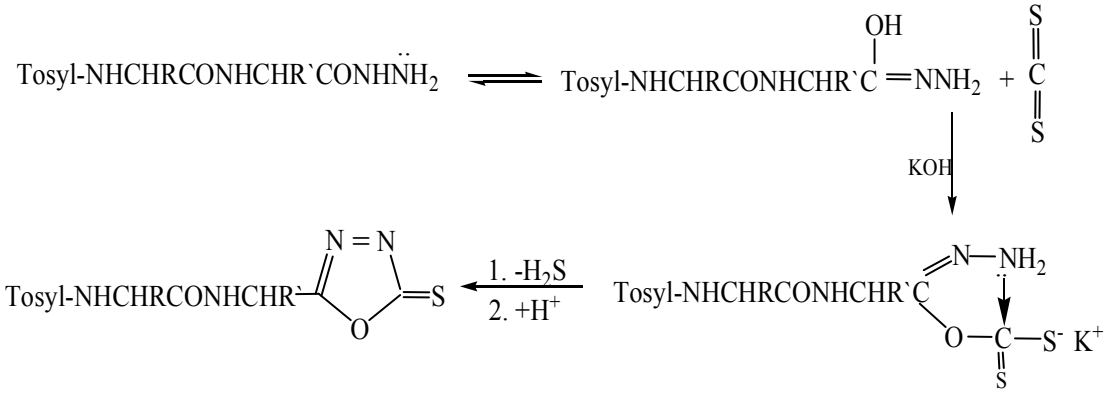
To a homogenous solution of hydrazones (7a-f) (0.01mole) in 20 ml of glacial acetic acid, PbO_2 (0.01mole) was added to the reaction mixture and stirred with mechanical stirrer at 25˚ C for 1 hrs. The reaction mixture was diluted with ice-water and left to stand for 24 hrs. The precipitate was filtered and recrystallized from benzene. (Table 2)

Results and discussion

Naproxen amino acid esters (3a-c) were synthesized from the reaction of naproxen and amino acid esters. Their IR spectra (Table1) shows the main absorption bands at 3306-3287 cm^{-1} for NH amide, 1710-1747 cm^{-1} for CO ester and 1670-1673 cm^{-1} for CONH stretching absorption. Naproxen amino acid amides (4a-c) synthesized through passing ammonia gas to a solution of naproxen amino acid esters in dichloro methane. They were characterized by the following absorption bands (Table2) 3303-3331cm^{-1} for NH stretching vibration and 1673cm^{-1} for CONH stretching vibration of amide in addition to absent of C=O ester stretching vibration.

Naproxen amino acid hydrazides (5a-c) were synthesized from the corresponding esters with hydrazine hydrate in absolute ethanol. The IR spectra shows the following main signals 3297-3331cm^{-1} for NH, 1627-1652 cm^{-1} for C=O stretching vibration.

Oxadiazoles have been prepared by many procedures (24-27). However in this investigation the preparation of oxadiazoles were achieved by two procedures. The first was performed by the reaction of hydrazides and carbon disulfide in alkaline medium. The mechanism of the reaction is accomplished by nucleophilic attack of the enol hydrazide form at the carbon atom of carbon disulfide. The formed xanthat salts underwent intra nucleophilic attack followed by hydrogen sulfide elimination to give oxadiazol -2-thione (28).



The IR spectra of compounds (6a-f) showed absorption bands at 3297-3444 cm^{-1} corresponds to the NH stretching vibration, and others gave the following vibrational absorption bands (1629-1702), (1605-1656), (1213-1295) and (1117-1196) cm^{-1} which are assigned to (C=O), (C=N), (C-O-C) and (C=S), respectively.

The second pathway of synthesis was by the reaction of hydrazide (5a-f) with p-chloro benzaldehyde to give the hydrazones (7a-f), the hydrazone were cyclized to oxadiazoles (8a-f) by their reaction in the presence lead dioxide, the hydrazones (7a-f) showed IR spectra at 3296-3445 cm^{-1} N-H, 1625-1672 cm^{-1} C=O and 1593-1640 cm^{-1} C=N stretching vibration.

The IR absorption spectra of oxadiazole (8a-f) showed the following bands (3290-3435), (1647-1672), (1605-1646) and (1205-1229) cm^{-1} assigned to NH stretching, C=O stretching, C=N stretching and combination band of C-O-C stretching vibrations, respectively.

The mechanism could be visualized according to following scheme:

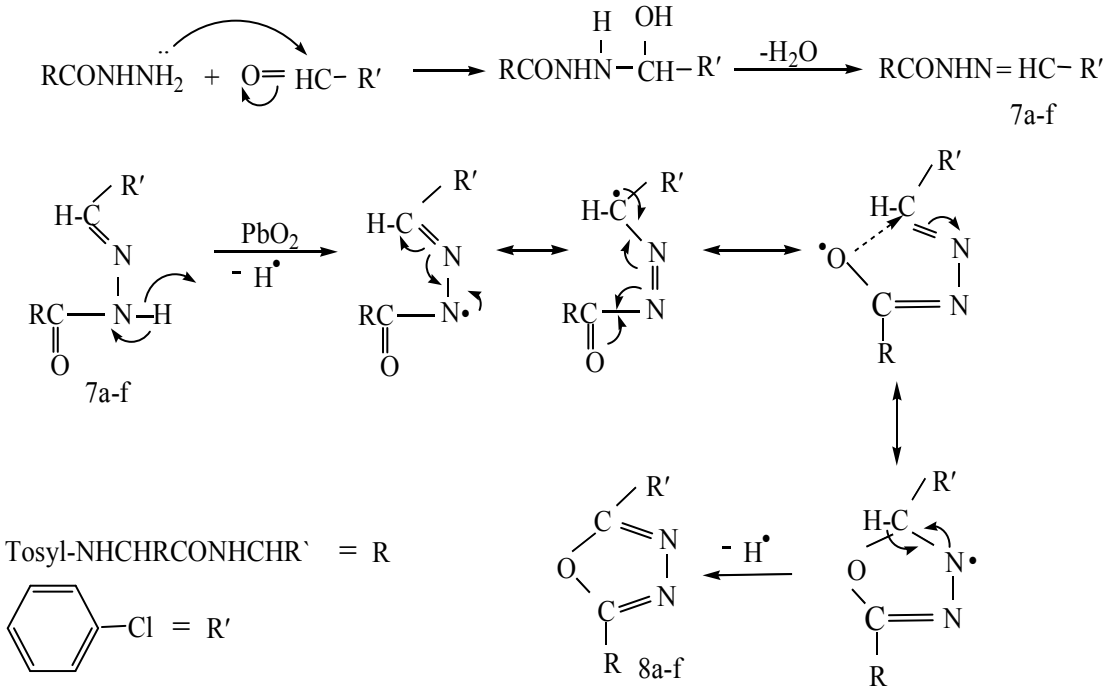


Table (1): Physical Properties and Spectral data of compounds amino acid Esters, amides and hydrazides

Comp. No.	M.P. °C	Color	Yield %	I.R. (KBr) cm^{-1}					UV $CHCl_3$ λ max nm
				υ_{NH}	υ_{C-H} arom	υ_{C-H} ali.	$\upsilon_{C=O}$ ester	$\upsilon_{C=O}$ amide	
3a	180-182	White	92	3287	3060	2930	1747	1673	333
3b	178-180	White	90	3306	3059	2932	1710	1673	330
3c	184-185	White	93	3306	3060	2932	1716	1670	332
4a	153-155	White	63	3306	3047	2930	----	1673	336

4b	189-192	White	68	3306	3050	2931	----	1673	333
4c	176-178	White	74	3303	3047	2931	----	1673	333
5a	125-127	Pale Brown	84	3331	3056	2929	----	1627	333
5b	172-174	Pale Brown	87	3292	3050	2933	----	1651	333
5c	152-155	Pale Brown	83	3297	3060	2930	----	1652	333

Table (2): Physical Properties and Spectral data of compounds (6a-f), (7a-f) And (8a-f)

comp. No.	M.P. ˚C	Color	Yield %	I.R.(KBr) cm^{-1}						UV $CHCl_3$ λmax nm
				υ_{NH}	$\upsilon_{C=O}$	υ C=N	υ COC	υC=S	υ Other	
6a	140-143	Peel yellow	67	3319	1629	1607	1213	1196	---	333
6b	170-173	Peel yellow	68	3297	1652	1607	1227	1118	–––	333
6c	168-171	Peel yellow	64	3324	1651	1627	1227	1170	–––	333
6d	175-177	yellow	66	3336	1702	1624	1243	1163	–––	350
6e	232-235	Peel yellow	66	3369	1672	1656	1295	1142	---	338
6f	183-185	Deep yellow	64	3444	1660	1625	1246	1117	3200 (OH)	342
7a	184-150	yellow	71	3303	1663	1640	–––	–––	–––	299
7b	168-171	yellow	66	3300	1652	1605	---	–––	–––	329
7c	172-174	Peel yellow	67	3323	1651	1627	–––	–––	–––	332
7d	210-212	yellow	61	3445	1625	1593	---	–––	–––	337
7e	224-226	Peel yellow	86	3290	1672	1646	–––	–––	---	292
7f	225-227	White	67	3286	1662	1610	–––	–––	3220 (OH)	312
8a	138-140	Brown	86	3327	1660	1628	1229	–––	–––	292
8b	143-145	Peel yellow	82	3299	1653	1605	1227	–––	–––	329
8c	130-132	White	75	3321	1650	1629	1227	–––	–––	285
8d	210-212	yellow	69	3435	1647	1625	1211	–––	–––	332
8e	238-240	Peel brown	85	3290	1672	1646	1205	–––	–––	306
8f	121-214	Peel brown	90	3340	1659	1625	1207	–––	3287 (OH)	332

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