Swift Journals 2060-2680

Swift Journal of Pharmacy and Pharmacology
Vol 1(1) pp. 011-015 January, 2016.
http://www.swiftjournals.org/sjpp

Original Research Article

Synthesis of Some New Oxadiazole and Tetrazole Derived from Naproxen Drugs

Huda A. Basheer[1], Maysoon S. Ahmed[1], Layla A. Othma[2]

[1]Chemistry Department / Faculty of Science / University of Zakho
[2]Chemistry Department/ Faculty of Science/ University of Duhok
Kurdistan region / Iraq

Accepted 23rd January, 2016.

ABSTRACT

Naproxen amino acid ester (2a-b) prepared by the reaction of naproxen with amino acid esters. Hydrazides (3a-b) were obtained by reaction of corresponding esters with hydrazine hydrate. These hydrazides were used to synthesize a series of five membered ring heterocyclic compounds, the hydrazides (3a-b) were converted to 1,3,4-oxadiazole-2-thione (4a-b) by their reaction with carbon disulfide in ethanolic potassium hydroxide. 2,5-Disubstituted 1,3,4-oxadiazole (6a-b) were obtained from the reaction of lead oxide with naproxen amino acid hydrazone (5a-b) where hydrazone prepared from the reaction of hydrazides (3a-b) with p-nitrobenzaldehyde. Mono substituted 1,3,4-oxadiazole (8a-b) were synthesized from the reaction of 2-formyl hydrazine (7a-b) with Phosphorous pentoxide. Finally, 4-amino 1,2,4-triazol-5-thiol (10a) was prepared from the reaction of dithiocarbazate salt with hydrazine hydrate. The structures of synthesized compounds were confirmed by physical and spectral means.

Keywords: Synthesis, Drugs, Hydraxide

INTRODUCTION

1,3,4-Oxadiazole are synthesized by cyclodehydration of N,N'-diacyl-hydrazines or their equivalents[1-2]. Katritzky and co-workers [3] have prepared 5-aryl-2-amino-1,3,4-oxadiazole compounds in excellent yields from the reaction between di(benzo-triazol-1-yl)methanimine and arylhydrazides. A convenient, one-pot procedure has been reported by condensing mono-aryl hydrazides with acid chlorides in HMPA solvent under microwave heating. Various hydrazides have been reacted with triethyl orthoalkanates or triethyl orthobenzoate, in the presence of Nafion NR50, under microwave irradiations and in the absence of any solvents to afford the desired 1,3,4-oxadiazoles in good yields[4]. Variety of disubstituted 1,3,4-oxadiazoles have been obtained by using POCl3[5], thionyl chloride[6], sodium hydroxide and iodine (as the oxidizing agent) in potassium iodide[7], carbon disulfide in ethanolic potassium hydroxide[8]. In this paper, we describe an approach to the preparation of oxadiazole derivatives of naproxen by several methods.

Experimental

Uncorrected melting points were determined by using bibby scientific limited stone, staffordishire, ST 15 OSA, UK., IR spectra was recorded as a KBr disc in the (400-4000 cm-1) range by using (spectrum one B FT-IR spectrometer).1HNMR spectra were measured with NMReady-60e from Nanalysis Company Made in USA. Hydrochloric acid, amino acid esters was prepared according to the reported procedure. [9]

Extraction of 2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen 500 mg)

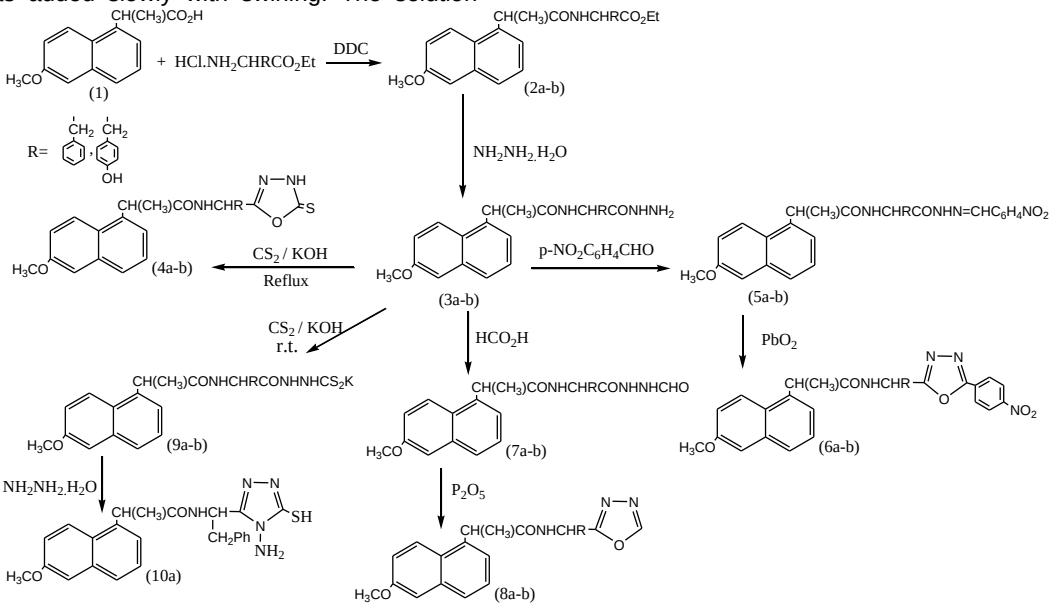
10 gm. of naproxen drug was grinded and dissolved in 50 mL of chloroform by stirring at room temperature for 1hr; filtered and evaporated to dryness and the precipitate was recrystallized from dichloromethane. The white crystals (70%) with melting point 153-155C◦, (published 152-154 °C)* were obtained [10]*.

Preparation of naproxen amino acid ester (2a-b)

Naproxen (0.0071 mole) was dissolved in 50 mL of tetrahydrofuran containing (0.0071 mole) of tri-n-butylamine.

Corresponding Author: Huda Ahmad Basheer, Chemistry Department / Faculty of Science / University of Zakho
E-mail: amal. caser.abdel@yahoo.com

The solution was then cooled to 0ºC and isobutylchloroformate (0.0071 mole) was added slowly with swirling. The solution was allowed to stand for 30 minute at 0 ºC.



To this mixture was added an ice cooled solution of amino acid ester hydrochloride (0.00592 mole) and (0.00592 mole) tri-n-butylamine in 100 mL of tetrahydrofuran. The reaction mixture was left for 24hrs at room temperature. The solvent was removed in vacuum and three volumes of water were then added. The product was extracted with ethyl acetate and washed with dilute hydrochloric acid, water, sodium bicarbonate (10%) and water. The ethyl acetate solution was dried on sodium sulfate, filtered, concentrated in vacuum and the residue was crystallized from ethyl acetate-petroleum ether [11].

Synthesis of naproxen amino acid hydrazide (3a-b)

A mixture of naproxen amino acid ester (0.01mole) (1a-b) and hydrazine hydrate (0.2mole) in absolute ethanol (70 mL) was refluxed for (3) hours. The solvent was evaporated under reduced pressure and the residue was recrystallized from Chloroform.

Synthesis of 5-(naproxen amino acid residue) -1,3,4-oxadiazole -2-thione(4a-b)

(0.05mole) of the naproxen amino acid hydrazide (3a-b) was dissolved separately in (70 mL) 0.5% ethanolic potassium hydroxide. (0.1 mole) of carbon disulfide was added gradually and the resulted mixture was refluxed for 16 hours until the evolution of hydrogen sulfide was ceased (checked by filter paper moister with lead acetate). The solvent was evaporated under reduced pressure and the residue was poured on crushed ice, diluted with ice-water, acidifies with diluted HCl, filtered and dried recrystallized from chloroform [8].

Synthesis of 4-nitrobenzaldehyde naproxen amino acid hydrazone (5a-b)

A mixture of p-nitrobenzaldehyde (0.01mole) and (0.01mole) of naproxen amino acid hydrazide (2a-b) in (20 mL) ethanol was refluxed for 2 hrs. The solvent was concentrated and the precipitate was filtered and recrystallized from benzene [12].

Synthesis of 2-(naproxen amino acid residue - 5-(4´-nitro phenyl) -1, 3, 4-oxadiazole (6a-b)

To a homogenous solution of hydrazone (5a-b) (0.01mole) in 20 mL glacial acetic acid, lead oxide (pbO2) (0.01mole) was added, the mixture was stirred at 25 C◦ for 1 hr. The reaction mixture was diluted with ice- water and left to stand for 24 hrs. The precipitate was filtered off and recrystallized from benzene [13].

Synthesis of 1-(naproxen amino acid) -2-formyl hydrazine (7a-b)

A mixture of (0.01mole) hydrazide (2a-b), formic acid (0.01mole) in absolute ethanol (20mL) was refluxed for 3hrs. The mixture was cooled and the precipitate was filtered, dried and recrystallized from ethanol.

Synthesis of 2-(naproxen amino acid residue)-1,3,4-oxadiazole (8a-b)

Phosphorous pentoxide (0.01 mole) was added to a solution (0.01mole) of compound (7a-b) in dry xylene (25 mL). The mixture was refluxed for 3 hrs, the solvent was evaporated and the residue washed with cooled water, dried and crystallized from ethanol.

Synthesis of potassium N-(naproxen amino acid residue) dithiocarbazate (9a-b)

A mixture of hydrazide (2a-b) (0.002mole) in solution of (0.0025mole) potassium hydroxide in 100mL of absolute ethanol and carbon disulfide (0.0025mole) were stirred at room temperature for 3hrs, the precipitate was filtered and recrystallized from ethanol.

Synthesis 3-(naproxen amino acid residue) 4-amino 1,2,4-triazol-5-thiol (10a)

A mixture of (0.01mole) of dithiocarbazate (9a) and (0.06mole) of hydrazine hydrate in (50mL) of absolute ethanol was refluxed for 5hrs, until observing change in the color of the mixture to green with liberation of hydrogen sulfide gas, the solution was cooled and acidified by diluted hydrochloric acid,

the precipitate was separated by filtration and recrystallized from ethanol-water.

Table 1: Physical and spectral data for compounds (2-10)

Comp.No.	R	M.P. ºC	Yield %	IR (KBr) υ cm^{-1}					
				C=O amide	C=O (C=S)	C=N	NH	OH	NO_2
2a	CH_2Ph	102-103	82	1637.5s	1722.3s	-	3446.2b	-	-
2b	$CH_2C_6H_4OH$	98-100	86	1643.2s	1726.9s	-	3320b	3446.2s	-
3a	CH_2Ph	215-216	88	1644.2s	-	-	3287.2s	-	-
3b	$CH_2C_6H_4OH$	236-237	93	1646s 1666.8s	-	-	3295.1	3410.7m	
4a	CH_2Ph	188-190	61	1654.8s	(1265s)	1605s	3409b	-	-
4b	$CH_2C_6H_4OH$	171-172	54	1637.2m	(1260m)	1600m	3412b	3438b	-
5a	CH_2Ph	217-218	56	1647.6s 1678.3s	-	1604.7s	3269.8s	-	1343.8s 1521.7s
5b	$CH_2C_6H_4OH$	239-240	58	1645.4s 1675.8s	-	1604.5s	3279s	3524.8s	1343.4s 1517.1s
6a	CH_2Ph	226-227	83	1645.2s	-	1604.3m	3278.9b	-	1343.1s1516.8s
6b	$CH_2C_6H_4OH$	239-240	38	1647.2s	-	1603.9m	3280.2w	3402w	1343.1s 1521.1s
7a	CH_2Ph	226-227	74	1644m	-	-	3202.1b	-	-
7b	$CH_2C_6H_4OH$	185-186	70	1645.8s	-	-	3199.1b	3411b	-
8a	CH_2Ph	260-261	56	1635m	-	1605.4s	3399.8b	-	-
8b	$CH_2C_6H_4OH$	245-247	81	1645.1s	-	1600m	3298w	3428.9b	-
9a	CH_2Ph	208-209	72	1643.1s	(1213.5s)	-	3413.2b	-	-
9b	$CH_2C_6H_4OH$	225-226	70	1645.9s 1666.8s	(1214.5s)	-	3295.3s	3416w	-
10a	CH_2Ph		71	1645.5s	(1236.3s)	1537.2m	3295.2s	-	-

Table (2): ^{1}H NMR spectral data of compounds (2a,3b,4a,9a,10a)

Comp. No.	R	^{I}H NMR
2a	CH_2ph	0.77-0.87 (d, 3H) CH$\underline{CH_3}$; 0.98-1.1 (t, 3H) $CH_2\underline{CH_3}$; 1.22-1.39(q, 1H)$\underline{CH}$ CH_3; 1.51(d, 2H) $\underline{CH_2}$ph; 3.84 (s, 3H)O$\underline{CH_3}$; 4 (q, 2H) O$\underline{CH_2}$; 4.11 (t,1H) NH$\underline{CH}CH_2$; 4.23(d, 1H)$\underline{NH}$CO; 7.24-7.85(m,11H) Ar-H
3b	$CH_2C_6H_4OH$	1.13(d, 3H) $\underline{CH_3}$CH; 1.26(s,1H)$\underline{CH}CH_3$; 2.48(d, 2H) $\underline{CH_2}$ph; 3.29 (q,1H) NH$\underline{CH}CH_2$, 3.83 (s,3H) O$\underline{CH_3}$; 4.15 (d,1H) $\underline{NH}$CHCO; 7.22 (d, 2H) NH_2; 7.41(d,1H) CO$\underline{NH}NH_2$; 7.6 (m, 10H)Ar-H; 7.81(s,1H)OH
4a	CH_2ph	1.04-1.16(d,3H) $\underline{CH_3}$CH; 1.27-2.47(q,1H) $\underline{CH}CH_3$; 3.09(d,2H) $\underline{CH_2}$CH; 3.09-3.35(q,1H) NH$\underline{CH}CH_2$; 3.82(s,3H) O$\underline{CH_3}$; 4.28(d,1H) COCH$\underline{NH}$; 4.4(s,1H) NH; 6.91-7.62 (m,11H)Ar-H
9a	CH_2ph	1.19(d,3H) $\underline{CH_3}$CH; 1.25-1.29(q,1H) $\underline{CH}CH_3$; 2.48 (d,2H) $\underline{CH_2}$ph; 3.28(q,1H) NH$\underline{CH}CH_2$; 3.84(s,3H) O$\underline{CH_3}$; 6.9(d,1H) CO$\underline{NH}$CH; 7.21(b,2H) 2NH, 7.64-7.79(m,11H) Ar-H
10a	CH_2ph	1.17 (d,3H) $\underline{CH_3}$CH; 1.21 (q,1H) $\underline{CH}CH_3$; 1.27(d,2H) $\underline{CH_2}$ph; 4.82(s,3H) OCH_3; 3.7(d,1H) CONHCH; 6.95 (s,1H) NH; 7.17(s,2H) NH_2; 7.36-7.83(m,11H) Ar-H

RESULT AND DISCUSSION

Naproxen amino acid esters (2a-b) have been prepared by the reaction of naproxen with amino acid ester (scheme 1), it was identified by IR spectra which showed the main absorption bands at (1637.5-1643.2)cm-1, (1722.3-1726.9)cm-1and (3446.2-3320)cm-1 assigned to C=O amide, C=O ester and NH respectively. The 1HNMR spectra for compound (2a) showed the following signals 0.77-0.87 (d, 3H) CHCH3; 0.98-1.1 (t, 3H) CH2CH3; 1.22-1.39(q, 1H)CH CH3; 1.51(d, 2H) CH2ph; 3.84 (s, 3H)OCH3; 4 (q, 2H) OCH2; 4.11 (t,1H) NHCHCH2; 4.23(d, 1H)NHCO; 7.24-7.85(m,11H) Ar-H.

Naproxen amino acid hydrazides (3a-b) were synthesized from the reaction of corresponding esters (2a-b) with hydrazine hydrate. Their structures were verified by IR spectra which showed the following main signals (1644.2-1646) cm-1 for C=O, (3287.2-3295.1) cm-1 stretching absorption together with the hydroxyl absorption band. The 1HNMR spectra for compound (3b) appeared the following signals 1.13(d, 3H) CH3CH; 1.26(s,1H) CHCH3; 2.48(d, 2H) CH2ph; 3.29(q,1H) NHCHCH2, 3.83(s,3H) OCH3; 4.15(d,1H) NHCHCO; 7.22(d, 2H) NH2; 7.41 (d,1H) CONHNH2; 7.6 (m, 10H) Ar-H; 7.81(s,1H) OH.

Oxadiazole -2-thione synthesis was performed by the reaction of hydrazides (3a-b) 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 [14].Compounds (4a-b) showed absorption bands at (1654.8-1637.2) cm-1, (1605-1600) cm-1, (1265-1260) cm-1, and (3412-3409) cm-1 related to C=O, C=N, C=S and NH respectively. The 1HNMR spectra for compound (4a) showed the following signals 1.04-1.16(d,3H)CH3CH; 1.27-2.47(q,1H)CHCH3; 3.09(d,2H)CH2CH; 3.09-3.35(q,1H)NHCHCH2; 3.82(s,3H) OCH3; 4.28(d,1H)COCHNH; 4.4(s,1H)NH; 6.91-7.62(m,11H)Ar-H.

Condensation of hydrazide (3a-b) with p-nitrobenzaldehyde gave hydrazone (5a-b), the hydrazone were cyclized to 2, 5-disubstituted -1, 3, 4- Oxadiazole (6a-b) by their reaction with lead dioxide, the hydrazones (5a-b) show IR spectra υ cm-1 at 1678.3-1647.6 (C=O), 1604.7-1604.5 (C=N), 3279-3269.8 (NH) and 1343.8-1343.4 & 1521.7-1517.1 (NO2), the oxadiazoles (6a-b) were characterized by main absorption bands for imine C=N and amide groups C=O at (1604.3-1603.9) cm-1 and (1647.2-1645.2) cm-1, while at (1516.8-1516.1) cm-1 and (1343.1) cm-1 represent NO2 asymmetric and symmetric stretching, respectively. The N-H groups of these compounds appeared broad bands at (3280.2-3278.9) cm-1. In order to synthesis mono substituted Oxadiazole, acid hydrazide (3a-b) was treated with formic acid to give 1-formyl-2-acyl hydrazine (7a-b) which transferred to substituted -1,3,4-oxadiazole (8a-b) by its reaction with PbO2.

Compounds (7a-b) were verified by IR spectra which showed the following main signals (1645.8-1644)cm-1 for C=O and (3202.1-3199.1)cm-1 while compounds(8a-b) showed absorption at (1645.1-1635)cm-1for C=O, (1605.4-1600)cm-1 for C=N and (3399.8-3298)cm-1 for NH. Dithiocarbazate salt (9a-b) was prepared from the reaction of hydrazide (3a-b) with carbon disulfide in alkaline medium at room temperature through the nucleophilic substitution reaction, which converted to 4-amino-1,2,4-triazol-5-thiol (10a) by hydrazine hydrate.

The IR spectra of dithiocarbazate salt (9a-b) showed the following stretching vibrational absorption bands, (1645.9-1643.1), (1214.5-1213.5) and (3413.2-3295.3) cm-1 assigned to C=O, C=S and NH respectively. The 1HNMR spectra for compound (9a) appeared the following signals 1.19(d,3H) CH3CH; 1.25-1.29(q,1H) CHCH3; 2.48(d,2H) CH2ph; 3.28(q,1H) NHCHCH2; 3.84(s,3H)OCH3; 6.9(d,1H)CONHCH; 7.21(b,2H)2NH, 7.64-7.79(m,11H)Ar-H. Compound (10a) showed 1645.5 cm-1 for C=O, 1236.3 cm-1 for C=S, 1537.2 cm-1 for C=N and 3295.2 cm-1 for NH whereas The 1HNMR spectra for compound (10a) showed the following signals1.17 (d,3H) CH3CH; 1.21 (q,1H) CHCH3; 1.27(d,2H) CH2ph; 4.82(s,3H) OCH3; 6.7(d,2H) CONHCH; 6.95(s,1H) NH; 7.17(s,2H) NH2; 7.36-7.83(m,11H)Ar-H.

REFERENCES

[1] C.J. Ainsworth, J. Am. Chem. Soc., 77, 1148, 1955.
[2] S.J. Dolman, F.O. Gosselin, P.D. O´Shea and I.W. Davies, J. Org. Chem., 71, 9548, 2006.
[3] A.R. Katritzky, V. Vvedensky, X. Cai, B. Rogovoy, P.J. Steel, ARKIVOC, 6, 82, 2002.
[4] V. Polshettiwar and R.S. Varma, Tetrahedron Letters, 49, 879, 2008.
[5] N. Sikder, N.R. Bulakh, A.K. Sikder, Ind. J. Heterocycl. Chem, 12, 29, 2002.
[6] S. Hernández-Ainsa, J. Barberá, M. Marcos, J. Serrano, Macro-molecules, 45, 1006, 2012.
[7] W.A. El-Sayed, O.M. Ali, H.A. Hendy, A.A.-H. Abdel-Rahman, Chin. J. Chem. 30, 77, 2012.
[8] R.A. Rashid, M.Sc. Thesis, University of Zakho, 2014.
[9] H. A. Basheer, , ph. D. Thesis, University of Mosul, 2000.
[10] www.scbt.com/datasheet-200506-naproxen.htmL
[11] M.S. Al-Ajely, H. A. Basheer, SH.KH. Younis, J. Edu. Sci., 2003, 15(2), 26-32.
[12] H. A. Basheer, Raf. J . Sci., 2002,13, 1,121.
[13] S. A. Mohamed, J. Edu. and Sci., 22, 2, 2009.
[14] M. H. H. Al-Juraisy, 2008, M.Sc. thesis, University of Mosul