International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.4, No.4, pp 1379-1382, Oct-Dec 2012

Synthesis of 4,5-Dihydro 1,3,4-Oxadiazoles And 1,3,4-Thiadiazoles Carrying Isatin Moiety

Hooshang Vahedi*,Jalil Lari, Abolfazl Housaini, Mohammad Habibi

Chemistry Department, Payame Noor University, 19395-4697 Tehran, I.R. of Iran, Iran.

Corres.author: hooshangvahedi@yahoo.co.uk
Tel.: +98 511 8683003-5; Fax: +98 511 868 3001.

Abstract: A practical two-step synthetic approach for 4,5-dihydro 1,3,4-oxadiazoles and 1,3,4-thiadiazole carrying isatin moiety is describedin good yield. The advantages of this procedure include short reaction steps, simple operation andgood yield.
Keywords*:*Isatin**,** 4,5-dihydro 1,3,4-oxadiazoles, 4,5-dihydro 1,3,4-thiadiazoles, acetic anhydride, semi carbazone and thiosemicarbazone.

Introduction and Experimental

Five membered heterocyclic compounds known to exhibit various types of biological activities, among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activities[1]. During the past years considerable evidences have accumulated to demonstrate the effectiveness of 1,3,4-oxadiazoles including antibacterial[2], anti-inflammatory[3], antimalarial[4], antitubercular[5], antihypoglycemic[6], anticancer[7], antileishmanial[8], antiviral[9], anticonvulsant[10] and insecticidal properties[11] .On the other hand, 1,3,4 -thiadiazoles are very interesting compounds due to their important applications in many pharmaceutical, biological and analytical fields[12,13] . Recently, the synthesis of novel 1,3,4-oxadiazole derivatives as potentialantimicrobial agents from the corresponding hydrazones using acetic anhydride has been reported[14] .In continuation of our work on the synthesis of heterocyclic systems containing nitrogen and sulfur[15], we describe here the synthesis of new 4,5-dihydro 1,3,4-oxadiazolesand 1,3,4-thiadiazoles carrying isatin moiety by the cyclization of the corresponding semicarbazones and thiosemicarbazones derivatives .

General

All chemicals were Aldrich analytical grade and were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer using TMS as the standard. CHNS analyses were obtained with a Thermo Finnigan Flash Elemental Analyzer; model 1112EA. FT-IR spectra were recorded on 8400 Model SHIMADZU FT-IR spectrometer (400-4000 cm^{-1}). Melting points were determined in open capillaries with a “Cintex” melting point apparatus and were uncorrected.

General procedure for the synthesis of imines 2a-2d

Isatin (0.01mol) and primary amine (0.01mol) in ethanol (30 mL) was stirred and heated at 70-75 ◦C and the progress of the reaction was monitored by TLC. The products were precipitated in high yields.

2a (0.69 g, 76%) m.p. 238-240 ^{o}C,^{1}H NMR (DMSO-d6): 6.68-7.67(m, 4H, Ar), 9.0 (s, 2H ,NH_2) , 11.0 (s, 1H, NH) , 12.4 (s, 1H, NH amide); ^{13}C NMR (250 MHz, DMSO) : =110.9 , 119.8 , 120.8 , 122.2 , 131.0, 131.9, 142.2, 162.5 (C=N) , 178.5, FT-IR (KBr disc) (cm^{-1}): 3238 and 3145

(NH_2), 3525 (NH) , 3055 (C-H) , 1687 (C=O) , 1610 (C=N) , 1134 (C=S); Anal .Calcd for $C_9H_8N_4OS$: C 56.04 , H 3.32 , N 23.06 , Found C 55.83 , H 3.76 , N 22.47.

2b (0.55 g, 74%) m.p. 260-262 ^oC, ^1H NMR (DMSO-d6): 7.0-7.6 (m, 6H, Ar and NH_2), 11.1 (s, 1H, NH) 11.7(s, 1H, NH); ^{13}C NMR (250 MHz, DMSO) : = 110.7, 120.2, 122.1, 130.2, 130.9, 141.3 , 154.9, 162.6 (C=N), 177.1 ; FT-IR (KBr disc) (cm^{-1}): 3303, 3134 (NH_2), 3469 (NH), 3004, 1708 (C=O), 1624 (C=N), 1575;Anal. Calcd.for $C_9H_8N_4O_2$: C 52.94, H 3.95, N 27.44; Found C 53.05, H 4.06, N 26.77.

2c(0.61 g, 67%) m.p. 166-168 ^oC,^1H NMR (DMSO-d6): = 6.92-8.41 (m, 10H, Ar and NH), 10.7(s, 2H, NH); ^{13}C NMR (250 MHz, DMSO): = 111.3, 115.8 , 122.3 , 125.5, 132.3, 143.3, 133.0, 155.8, 165.1 (C=N); FT-IR (KBr disc) (cm^{-1}): 3475, 3211, 3130, 1720 (C=O), 1691 (C=O) , 1602 (C=N);Anal. Calcd.for $C_{10}H_8N_2O_3$: C 58.83 , H 3.95 , N 13.72; Found C 59.11 , H 4.62 , N 13.27.

2d (0.79 g, 64.5%) m.p. 264-266 ^oC, ^1H NMR (DMSO-d6): = 6.90-7.62 (m, 10H,Ar and NH) , 11.34 (s, 2H, NH);^{13}C NMR (250 MHz, DMSO): =112.0 ,117.7, 121.1, 124.5, 130.8, 138.2, 132.0, 162.5 (C=N) , 175.1; FT-IR (KBr disc) (cm^{-1}): 3232 (NH) , 3078 , 1737 (C=O) , 1699 (C=S) 1618 (C=N);Anal .Calcd for $C_{17}H_{12}N_6O_2$: C 56.04 , H 3.32 , N 23.06; Found C 55.83 , H 3.76 , N 22.47.

2e (0.63 g, 71%) m.p. 316-318 ^oC, ^1H NMR (DMSO-d6): = 6.8-8.3 (m, 11H, Ar and NH) , 10.7 (s, 2H, NH);13C NMR (250 MHz, DMSO): =110.2 , 116.4 , 121.2 , 126.0 , 130.3 , 143.3, 131.0 , 159.9 (C=N) , 165.0 (C=O) ; FT-IR (KBr disc) (cm^{-1}): 3172 (NH) , 3064 (C-H) , 1703 (C=O) , 1618 (C=N) , 1577 , 1461 , 1514 , 1097 ;Anal .Calcd for $C_{17}H_{13}N_7O_2$: C 53.2 , H 3.68 , N 25.55 ; Found C 52.63 , H 4.40 , N 24.83.

General procedure for the synthesis of imines 3a-3d

To the imines (**2a-2d**) (0.3 g) in a round-bottom flask was added acetic anhydride (10 mL) and heated under reflux for 4 hrs. The solution is then allowed to cool and was poured on ice, dropwise. After adding chloroform (10 mL) the organic face was separated, dried on sodium sulphate, filtered and evaporated the solvent to yield the crude product which was purified by crystallization from methanol.

3a; (0.26 g, 60.69%), m.p. 165-170 ^oC, ^1H NMR (250 MHz;$CDCl_3$): 12.2 (s, 2H, ArNH), 7.8 (s, 2H, CNHCO), 6.6-7.8 (m, 4H, Ar), 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3): ^{13}C NMR (250MHz, $CDCl_3$) 19.5, 26.6, 116.8, 119.8, 125.4, 125.6, 130.6, 131.3, 140.1, 144.4, 161.2, 169.9, 173.7 FT-IR (KBr) (cm^{-1}):1666 and 1712 (C=O), 1616 (C=N); Anal .Calcd for $C_{13}H_{12}N_4O_3S$: C 51.31, H 3.97, N 18.41; Found C 51.25, H 3.24, N 18.31.

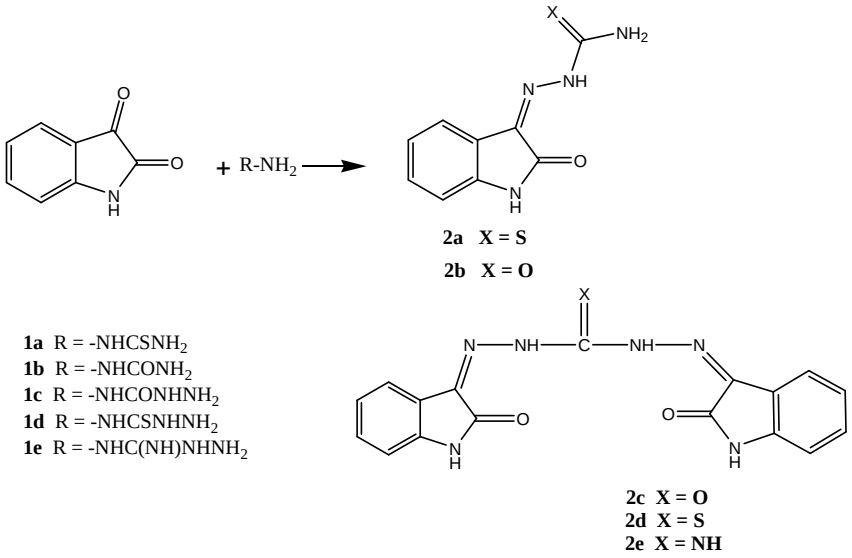
3b (0.27 g, 61.6%), m.p. 172-175 °C,^1H NMR(250 MHz;$CDCl_3$): 7.21-7.81(m, 4H, Ar), 12.2 (s, 2H amide) 2.6 (s, 6H, CH_3); ^{13}C NMR (250MHz, $CDCl_3$) 19.5, 26.6, 116.9, 119.9, 120.5, 125.6, 130.6, 131.3, 140.0, 144.5, 161.1, 169.9, 173.7; FT–IR (KBr) (cm^{-1}): 1157, 1610, 1680 and 1740 (C=O), Anal. Calcd for $C_{13}H_{12}N_4O_4$: C 54.17 , H 4.20 , N 19.44;Found C 54.25, H 4.24, N 19.31.

3c; (0.28 g, 77.7%) m.p. 245-247 °C, ^1H NMR (250 MHz;$CDCl_3$): 12.2 (s, 1H, NH) 13.8 (s, 1H, NH) 6.8-7.8 (m,8H, Ar), 2.7 (s, 6H, CH_3) 2.8 (s, 6H, CH_3); ^{13}C NMR (250MHz, $CDCl_3$) 24.6, 26.6, 116.9, 117.1, 119.9, 120.4, 123.9, 125.6, 126.2, 126.5, 130.4,131.0, 131.3, 139.2, 149.2, 162.1, 162.8, 168.6, 169.9, 170.7, 172.6; FT–IR (KBr) (cm^{-1}):1604, 1712 (C=O) , 1157 (C-O) Anal. Calcd for $C_{21}H_{16}N_6O_5$: C 58.34 , H 3.72 , N 19.44;Found C 58.98, H 3.84, N 18.95.

3d; (0.29 g, 79.3%) m.p. 211-215 °C; ^1H NMR (250MHz; $CDCl_3$) : 12.7 (s, 2H, NH) 6.84-7.5 (m, 8H, Ar) 2.6 (s, 3H, CH_3) 2.2 (s, 3H, CH_3) ; ^{13}C NMR (250 MHz,$CDCl_3$): 22.1, 26.5, 116.8, 117.0, 119.6, 120.0, 123.9, 125.7, 126.1, 126.4, 130.3, 131.0, 131.2, 139.1, 149.2, 162.1, 162.7, 168.5, 169.8, 170.5, 172.6; FT–IR (KBr) (cm^{-1}):1666, 1712 (C=O), 1616 (C=N); Anal. Calcd for $C_{21}H_{16}N_6O_4S$: C 56.34 , H 3.60 , N 18.74; Found C 56.32 , H 3.82, N 17.82.

Results and discussion

The semicarbazones and thiosemicarbazoneswere prepared from isatin (Scheme 1). The mixture of indoline-2,3-dione (0.01mol) and primary amine (0.01mol) in ethanol was stirred at 70-75 ^oC and the progress of the reaction was monitored by TLC. The products were precipitated in high yield.The structure of the imines 2a-2e was assigned based on NMR, MS, and IR data as well as elemental analysis.The absorption band around 1600 cm^{-1}(C=N) and signals around 160 ppm in the ^{13}C NMR spectrum are characteristic for the preparation of the products.

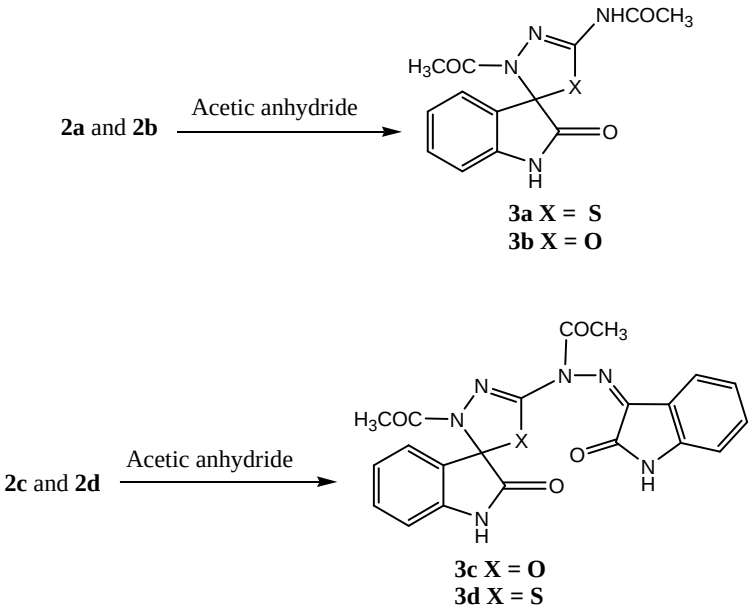


Scheme 1: The synthesis of imines 2a-2e

The imines 2a-2d were refluxed with acetic anhydride to give crude 4,5-dihydro 1,3,4-oxadiazoles and 1,3,4-thiadiazoles derivatives of 3a-3d which were purified by crystallisation in moderate to high yields.However, the reaction of 2e under a same reaction conditions as for 2a-2d, gave a complex mixture. All attempts to purify the mixture by column chromatography or crystallization using different solvent combinations proved fruitless. The structures of 3a-3d were deduced from its elemental analyses and its IR, ^{1}H and ^{13}C NMR spectra. IR spectrum showed absorption bands in the regions of 1712-1740 cm^{-1}(C=O), 1604-1616cm^{-1}(C=N). The ^{13}C NMR of the compounds exhibited four lines for the carbonyl and imine functional groups at 160-175 ppm along with two signals formethyl at about 19-26 ppm.

Acknowledgment

We are grateful to the Research Council of Payame Noor University, I. R. of Iran, for the financial support of this work.



Scheme 2: Synthesis of 4,5-dihydro 1,3,4-oxadiazoles and 1,3,4-thiadiazoles

References

1. Shaharyar M. and WasimAkhte M.,Synthesis and Anticonvulsant activity of substituted oxadiazole and thiadiazole Derivatives, ActaPoloniae Pharm. Drug Res.,2009, 66, 393.
2. Xin-Ping H., Lin-Mei Z. andZi-yi Z.,Synthesis and antibacterial activities of 1,3,4-thiadiazole, 1,3,4-oxadiazole and 1,2,4-triazole derivatives of 5-methyl isooxazole, Indian J. Chem.,1999**,** 38B, 1066.
3. Sharma S.,KishorV.S. andKumar A.,Synthesis of some newer indolyl-thiadiazolylpyrazolines and indolyl-oxadiazolylpyrazolines as potentials anti-inflammatory agents, Indian J. Chem.,2002**,** 41B, 2647.
4. Mogilaiah K.,Ramesh B.H. andBabuRao R.,Synthesis and antimicrobial activity of somenew 1, 3, 4-oxadiazolyl-1,8-naphthyridines, Indian J. Heterocyclic Chem.,2000, 10,109.
5. Dhoel S.R., Bhimani A.S., Khunt R.C. and Parikh A.R.,Synthesis of certain 1, 3, 4-Oxadiazoles as potential antitubercular and antimicrobial agent, Indian J. Heterocyclic Chem.**,**2005, 1, 3.
6. GoankarS.L.,RaiK.M L. and Prabhuswamy B.,Synthesis and antimicrobial studies of a new series of 2-{4-[2-(5-ethylpyridin-2-yl) ethoxy] phenyl} -5-substituted-1,3,4-oxadiazoles, Eur. J. Med. Chem.**,**2006,41, 841.
7. SenguptaP.,Deepak KumarD.,Yeligar C.V., MurugeshK., RajalingamD., JagadishS. And Maity T.K., Evaluation of anticancer activity of some 1, 3, 4-oxadiazole derivatives, Indian J. Chem.**,**2008**,** 47B, 460.
8. RastogiN., RajendraS.; Shukla,S.;Sethi, R. Microwave mediated aminomethylation and antileishmanial activity of 2-{4 '-(2",4"-dichlorobenzyloxy)-phenyl}-1,3,4-oxadi azolin-5-thiones and 3-{4'-(2",4"-dichloro benzyloxy)-phenyl}-4-phenyl-1,2,4-triazolin-5-thiones, Indian J. Heterocyclic Chem.,2006, 5, 16.
9. KarthikeyanM., JagadeeshP., Mahalinga D. Shivarama B.H. andSuchethaN.K., Anti microbial studies of 2,4-dichloro-5-fluorophenyl containing oxadiazoles, Eur. J. Med. Chem.**,** 2008**,** 25, 43.
10. PatilR. And Biradar J.S.,Synthesis and biological activities of new 3,5-disubstituted-2-(ethyl-5'thioxo-1',3',4'-oxadiazol-4'-ethylacetate-2'-yl)indoles, 2-(5'thioxo-1', 3', 4'-oxadiazol-4'-methylcarboxy hydrazide-2'-yl) indoles and2-(5'-thioxo-1',3',4'-oxadiazol-4'-alkyl-2'-yl) indoles, Indian J. Chem.,1999**,** 38B, 76.
11. MohanT.P.,VishalakshiB.,BhatK.S.,RaoK.S. andKendappaG.N.,Synthesis andinsecticidal activity of some 1,3,4-oxadiazolederivatives containing phenoxyfluorophenyl group, Indian J. Chem.,2004**,** 43B, 1798.
12. KornisG., Comperhensive Heterocyclic Chemistry, Oxford, 1984,575.
13. Ahmed, M.; Jahan, J.I.; Banoo, S. Asimple spectrophotometric methods for the determination of Cu in industrial, environmental,biological and soil, samples using2,5-dimercapto1,3,4-thiadiazole, Anal. Sci.**,**2002**,**18,805.
14. a)CaoS.,QianX.,SongG. And Huang Q., Synthesis and insecticidal activity of new2-(5-(trifluoromethyl)pyridyl oxymethyl)-1,3,4-oxadiazoles, J. Fluorine Chem.**,**2002**,** 63, 117. b)Chawla R.,AroraA. And Kumar M., ActaPoloniae Pharm. Drug Res.**,**2010**,** 67, 247.
15. a) NamiN.,GholamiF.,VahediH. andNamiN., Synthesis of thiadiazine and triazino[3,4-b]thiadiazine derivatives, Phosporus Sulfur Silicon Relat. Elem.**,**2007**,**182,2157. b)VahediH.,NamiN. andNamiN.,Synthesis and structure elucidation of4-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl-methylene)-2-phenyl-1H-imidazol-5(4H)-one, E-J Chem.**,** 2010**,**7,1116. c)Hakimi M., Vahedi H., Rezvaninezhad M.,Schuh E. And Mohr F., Synthesis and characterization of copper(I) complexes from triphenylphosphine and isatin Schiff bases of semi- and thiosemicarbazide, J. Sulfur Chem.,2011**,** 32**,** 55.

*****