Heterocyclic Letters
Vol. 9| No.4|411-416|Aug –Oct |2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF SUBSTITUTED THIOUREA ON AZETIDIN-2-ONE MOIETY AND THEIR ANTIOXIDANT ACTIVITY

FARHANULLAH A. KHAN[*1], RAHIM S.SHEIKH[1]

Department of Chemistry,
Govt. Vidarbha Institute of Science and Humanities, Amravati, Maharashtra, 444604-India.
E-mail: farhankhan085@gmail.com

Abstract: It was thought interesting to synthesized derivative of thiourea. A simple and efficient procedure for the synthesis of substituted thiourea. In this work new substituted thiourea have been reported from 3-chloroazetidin-2-one. 3-chloro azetidin-2-one in turn were obtained from schiff base which product of substituted aldehyde and substituted aniline in presence of H_2SO_4. The newly synthesized compound were fully characterized by spectroscopic data and screened for their in vitro antioxidant activity using 1,1-diphenylpicrylhydrazyl (DPPH) radical scavenging methods by this method. Thus the title compounds are a new class of potent antioxidant agent and worthy of further investigation.

Keywords: N-[(E)-furan-2-ylmethylidene]-3-nitroaniline, 3-chloro-substituted azetidin-2-one, antioxidant, phenylthiourea, DPPH.

Introduction

Thiourea is the analogue compound to urea with replacement of oxygen atom in urea by sulphur atom, also thiourea have a considerably wide range of applications. The properties of urea and thiourea differ significantly because of the difference in electronegativity between sulfur and oxygen[i]. Many thiourea derivatives are of pharmacological importance like anti-HIV. Antiviral[ii,iii], antitubercular[iv,v], Analgesic [vi] and anticancer properties[vii,viii]. In addition, urea and thiourea have emerged as structurally novel anticonvulsant [ix]. Derivatives of Thiourea also shows antimicrobial and antifungal activity[x,xi]. Derivatives of thiourea possessing good biological activities like antiviral, antibacterial, antifungal, antitubercular, anti-thyroidal, herbicidal and insectidal[xii,xiii,xiv,xv]. These are also found as precursors or intermediates in the synthesis of a variety of heterocyclic system. Further nitrogen and sulphur donor atoms in thiourea provide a multitude of bonding possibility, hence, its derivatives are versatile ligands and able to coordinate to metal centers either as neutral ligands, mono anions or di-anions and form stable complexes [xvi]. Thiourea and its derivatives are used as corrosion inhibitors in industrial equipment such as boiler [xvii]. It has various agricultural [xviii] and analytical applications which include applications in rubber industries as accelerators [xix]. Thiourea is one the most important compounds used in

relation to metallic electrode [xix]. It can absorb to a metal surface and in so doing block active sites[xx]. It is also one of the most important industrial chemical products[xxi].

Materials and Methods:-

Substituted aldehyde, substituted aniline, Triethylamine, Chloroacetylchloride, Dioxane are required chemicals purchased from s-d fine chemicals and phenylthiourea were sigma-aldrich. All the used chemicals were A.R grade, melting point were measured in open capillary tube and are uncorrected. The purity of the compounds was check by TLC on silica gel in petroleum ether and ethyl acetate [80:20] and the spots were located under iodine vapours as visualised agent. The IR spectra were recorded on Agilent technology. H^1-NMR was recorded on Bruker AVANCE 400 MHZ spectrometer using TMS as an internal standard.

Experimental Methods:-

In this work, new substituted Schiff base were prepared by condensation of the substituted aldehyde and substituted aniline in ethanol in presence of H_2SO_4. Schiff base thus obtained were further condensed with chloroacetylcloride and Triethylamine in dioxane to afford the formation of 3-chloro-substituted azetidin-2-one.3-chloro-substituted azetidin-2-one was refluxed with phenylthiourea in isopropanol.

Scheme-I

Synthesis of N-[(E)-furan-2-ylmethylidene]-3-nitroaniline:

Furfural and 3-nitroaniline were taken in equimolar (0.03mol) proportion and dissolved in ethanol. To this solution added 2-3 drops of H_2SO_4. The reaction mixture was refluxed for four six. Solid mass obtained was filtered and recrystalised from ethanol.

Yield : 64%
Melting point : 136^{0}C
Molecular formula: $C_{11}H_8N_2O_3$
IR: 3103 cm^{-1} (Ar, C-H str); 1415cm^{-1} (Ar, C=C str); 1506cm^{-1}(C=N str);
1111 cm^{-1} (C-O str); 1315-1506 cm^{-1} (-NO_2 asy str).
H^1-NMR: 7.80 (s, 1H, Ar-H); 7.66(dd, 1H, Ar-H); 7.32(dd, 2H, Ar-H); 8.50(s, 1H, CH); 7.84(d, 1H, CH); 6.8(dd, 1H, CH); 6.93(d, 1H, CH)

Scheme-II

Synthesis of 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl)azetidin-2-one.

N-[(E)-furan-2-ylmethylidene]-3-nitroaniline and Triethylamine were taken in equimolar (0.03mol) proportion and dissolved in 1,4-dioxane. Maintained the temperature of the solution up to 5 to 15°C, chloroacetylchloride (0.002mol) was added drop wise within a 15 minutes. The reaction mixture was then stirred on magnetic stirrer for 3 hours then poured into ice cold water. The product was purified by column chromatography over silica gel coated plates by using ethyl acetate. Recrystallized the product from ethanol.

Yield : 77 %
Melting point: 154°C
Molecular formula: $C_{11}H_8N_2O_3$
IR: 3107 cm^{-1} (Ar, C-H str); 1502cm^{-1} (Ar, C=C str); 599.86 cm^{-1} (C – Cl str);
1712cm^{-1}(C=O str); 1239.37cm^{-1} (C-N str); 1180.44 cm^{-1}(C-O str); 1301-1502 cm-1 (-NO_2 asy str).

H^1-NMR: 8.11 (s, 1H, Ar-H); 7.62(dd, 1H, Ar-H); 8.14(d, 1H, Ar-H); 5.44(d, 1H, CH); 7.56(d, 1H, CH); 6.39(dd, 1H, CH) ; 6.43(d, 1H, CH); 5.39(d, 1H, CH)

Scheme-III

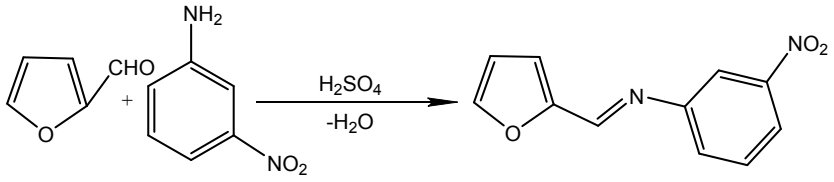
Synthesis of 1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-phenylthiourea.

A reaction mixture of 3-chloro substituted azetidin-2-one and phenyl thiourea were taken in equimolar (0.03mol) proportion in isopropanol medium was refluxed for 4 hours on water bath, brown crystals were separated out at room condition, filtered and dried. It was recrystallize of aqueous ethanol. Completion of reaction was monitoring by TLC.

Yield : 73 %
Melting point: 184°C
Molecular formula: $C_{15}H_{13}N_4O_4S$
IR : 3176.76 cm^{-1} (Ar, C-H str); 1523cm^{-1} (Ar, C=C str); 1693(C=O str); 1230.09cm^{-1} (C-N str); 1170.79 cm^{-1}(C-O str) ; 1346-1487 cm^{-1} (O=N asy str); 2126 cm^{-1}(C=S).
H^1-NMR : 8.10 (s, 1H, Ar-H); 7.42(dd, 1H, Ar-H); 8.14(d, 1H, Ar-H); 5.44(d, 1H, CH); 7.56(d, 1H, CH); 6.39(dd, 1H, CH) ; 6.43(d, 1H, CH); 5.39(d, 1H, CH); 7.3(q, 1H, NH); 2.8 (d, 3H, CH); 9.4 (d, 1H, NH)

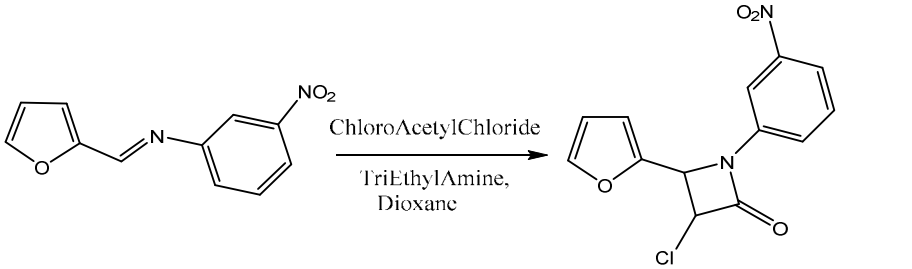
REACTION

SCHEME-1: Synthesis of N-[(E)-furan-2-ylmethylidene]-3-nitroaniline:



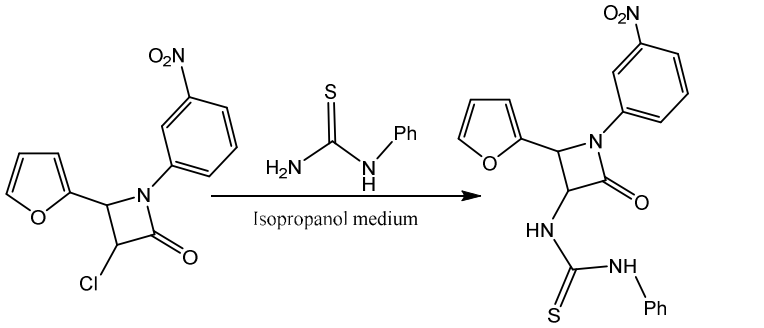
N-[(E)-furan-2-ylmethylidine]-3-nitroaniline

SCHEME -II: Synthesis of 3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one.



3-chloro-4-(furan-2-yl)-1-(3-nitrophenyl) azetidin-2-one

Scheme-III:-Synthesis of 1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-phenylthiourea



1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3-phenylthiourea

Anti-Oxidant Activity:-

***In vitro* Methods**

DPPH Radical Scavenging Activity

Procedure: To 1ml of DPPH solution, equal amount of test compound at various concentrations (20-100 ug/ml) were added in a final volume of 2.0 ml. After incubation for 20 minutes at room temperature, absorbance due to changes in color from deep violet to light yellow were recorded at 517 nm. The control solution was prepared by mixing ethanol (3.5 mL) and DPPH radical solution (0.3 mL). Lower absorbance of the reaction mixture indicated higher free radical activity. The experiment was performed in triplicate.

Calculation:

Percentage Scavenging activity = Absorbance of Control – Absorbance of sample/ Absorbance of Control × 100

CONTROL:-

Concentration	**Absorbance**
Ethanol (3.5 mL) and DPPH radical solution (0.3 mL)	1.02

STANDARD: (Ascorbic acid)-

Concentration	**Absorbance**	**Percentage scavenging activity**
20 ug */ml*	*0.931*	*8.73*
40 ug */ml*	*0.658*	*35.41*
60 ug */ml*	*0.581*	*43.03*
80 ug */ml*	*0.414*	*59.41*
100 ug */ml*	*0.381*	*62.64*

SAMPLE:-

Concentration	**Absorbance**	**Percentage scavenging activity**
20 ug */ml*	*0.710*	*30.39*

40 ug */ml*	*0.401*	*60.68*
60 ug */ml*	*0.361*	*64.60*
80 ug */ml*	*0.325*	*68.13*
100 ug */ml*	*0.196*	*80.78*

RESULTS AND DISCUSSION

We synthesized here unreported 1-(2-(furan-2-yl)-1-(3-nitrophenyl)-4-oxoazetidin-3-yl)-3- phenylthiourea by the interaction of 3-chloro substituted azetidin-2-one and phenyl thiourea. 3-chloro substituted azetidin-2-one was obtained by condensation of N-[(E)-furan-2-ylmethylidene]-3-nitroaniline, triethylamine and chloroacetylchloride. N-[(E)-furan-2-ylmethylidene]-3-nitroaniline was obtained by the condensation of substituted aldehyde and substituted aniline in presence of H_2SO_4.

CONCLUSION

Thus it was possible for us to reduce reflux time and increase percent yield of new synthesized products. The use of triethylamine as a base afford rapid synthetic route to azetidin-2-one and also easy workup of the products. These newly synthesized compounds with change method contain many bioactive substituents and therefore should be screened for their antioxidant activity.

ACKNOWLEDGEMENT

The authors are thankful to the authority of G.V.I.S.H., Amravati for providing laboratory facilities and VIT for analytical data, Govt Pharmacy college, Amravati for antioxidant activity.

REFERENCE

i. C. Alkan, Y. Tek, D. Kahraman., *Turk J Chem*, **2011**; 35: 769-777.
ii. Bell FW, Cantrell AS, Hogberg M, Jaskunas SR, et al., *J Med Chem,* **1995**; 38(25): 4929- 4936
iii. Kucukguzel I, Tatar E, Kucukguzel SG, Rollas S, DeClercq E., *Eur J Med Chem*, **2008**;43(2):876-878.
iv. Sriram D, Yogeeswari P, Madhu K.,*Bioorg Med Chem Lett*, **2006**; 16: 876-878.
v. Saeed A, Shaheen U, Hameed A, Haider Naqvi SZ., *J of Fluor Chem*, **2009**; 130(11):1028-1034.
vi. Dos Santos L, Lima LA, Cechinel-Filho V, Correa R, BuzziFC, Nunes RJ., *Bioorg Med Chem,***2008**; 16:8525-8534.
vii. Karakus S, Kucukguzel SG, Kucukguzel I, DeClercq E, Panneccouque C, Andrei G, et al.,*Eur J Med Chem*, **2009**; 44(9):3591-3595.
viii. Liu J, Song B, Fan H, Bhadury PS, Wan W, Yang S, et al., *Eur J Med Chem*, **2010**; 45(11):5108-5112.
ix. Siddiqui N and Alam MS., *Der Pharma Chemica,* **2010**; 44(2):115-137.
x. Monika R. Thakur and Shirish P. Deshmukh., *Rasayan J. Chem*, **2015**; 8(9):471-476.
xi. Viraj Pareshbhai Jatakiya, Kiran Manubhai Patel, Ravikumar V.Modi, Dr. R. Badmanaban and Dr. Dhrubo Jyoti Sen., *International Journal of Drug Development and Research*, **2011**; 3(4):294-299.
xii. Stefanska J, Szulczyk D, Koziol A E AND Miroslaw B., Eur. *J. Med.Chem*, **2012** 55, 205.
xiii. Yonova P A and STOILKOVA G M, *J. Plant Growth Regul*, **2005**; 23: 280

xiv. H.S. PATEL and H.D. DESAI., *E-journal of chemistry*, **2004**; 1**:**194.
xv. G. Madhavaa, K. Venkata Subbaiahb, R. Sreenivasulu, C. Naga Raju*, Der Pharmacia Lettre,***2012**; 4:1194-1201.
xvi. Katla Ramana Venkata, Rasheed Syed, Golla Madhava, Shaik Adam, Naga Raju,*J. Serb.Chem.Soc*,**2014**; 79:283-289.
xvii. B.K.Banik and I. Becker., *Bioorg. Med. Chem*, **2005**; 13**:** 3611.
xviii. Takai S, S. Jin, Muramatsu, M. Okamato, Y. Miyazaki*., M.Pharmaco*, **2004**; 1:501.
xix. Kohli, P. Srivastava, S.D. Srivastava*., Journal of Indian Chemical society*, **2008**; 85: 326.
xx. Zhao J and Cui G., *International Journal of Electrochemical Science*, **2011**; 6:4048-4058.
xxi. Yahyazahed A and Ghasemi Z., *European Chemical Bulletin*, **2013**; 2(8):573-575.

Received on September12. 2019.