Synthesis of some Heterocyclic Compounds Derived from 2-Chloro-N-p-Tolylacetamide

Hanan Gh. Shaaban
Department of Chemistry, College of Science, Al-Mustansiriyah University, Iraq.

A r t i c l e i n f o
Received
12/10/2015
Accepted
5/6/2016

Keywords:
Hetroylic,
p-aminotoluene,
aromaticaldehydes,
Sshiff bass,
β-lactam

ABSTRACT

This research includes preparation of (2-chloro-N-p-tolylacetamide) (1) from the reaction of (p-aminotoluene) with chloro acetyl chloride. Compound (1) reacted with thiosemi carbazide and gave compound (2), and when compound (1) reacted with semicarbazide gave compound (3). While when compound (1) reacted with thiourea it produced compound (4).

Compounds (2-4) when reacted with appropriate aromatic aldehydes or ketones produced Shiff bass (5-16), which in turn reacted with chloro acetyl chloride in the present of tri ethyl amine and dioxin gave β-lactam derivatives (14-22). The structures of these compounds were characterized from their melting points, FT-IR, and NMR.

الخلاصة

يتضمن البحث تحضير المركب (2-كلورو-N-بارا-توليل أسيد أمايد) (1) من تفاعل بارا أمينو تولوين مع كلورو أسيتايل كلورايد، عند مفاعلة المركب (1) مع ثايوسيميكارابازايد نتج المركب (2) في حين أن المركب (1) عندما تفاعل مع سيميكاربازايد أنتج المركب (3). أما عندما تفاعل المركب (1) مع ثايويوريا فقد أنتج المركب (4).

بعد تفاعل المركبات (2) و(3) و(4) مع ألديهايدات أو كيتونات أروماتية مناسبة نتج قواعد شف (5-13) التي تفاعلت بدورها مع كلوروأسيتايل كلورايد بوجود الدايوكسان وثلاثي أثيل أمين وأنتجت مشتقات البيتا لاكتام (14-22). شخصت هذه المركبات من خلال درجات الإنصهار وتقنيات FT-IR وNMR.

INTRODUCTION

The synthesis of oxazole compounds has attracted a great deal of attention due to its widespread application of oxazole derivatives in biologically active compounds [1, 2]. It displays antiviral, antifungal [3], antibacterial and anti-proliferative activities [4].

Substituted axazole derivatives synthesis is particularly important because of compounds involving the oxazole ring system are known to have diverse range of biological activities in pharmaceutical areas [5].

The thiazole chemistry has been extensively developing because of their unique physiological properties[6].

The thiazole ring is presented in a variety of therapeutic agents; these agents can exhibit significant anti-cancerous, antimicrobial, antidiabetic, anti-inflammatory, antiviral or analgesic activity [7].

Schiff bases derived from various heterocyclic compounds displayed a broad range of biological activities such as antidepressant, anti-glycation. So far, modifications of Schiff bases have proven highly effective with improved potency and lesser toxicity [8].

The β-lactam heterocyclic is the key structural unit of the most widely used β-lactam antibiotics [9-11].

The biological activity of β-lactam as cholesterol acyl transferas inhibitors [12], thrombin inhibitors [13], antitumor [14], the ring in β-lactam have also antimicrobial properties [15].

MATERIALS AND METHODS

Melting points were measured using Gallen Kamp melting point apparatus, and were uncorrected. The FT-IR spectra of the prepared compounds were recorded using Shimadzu FT-IR 8300 spectrophotometer as KBr disc in Al-Mustansiriyah University, results are given cm^{-1}.^{1}H.NMRspectra were recorded on Bruker spectro spin ultra-shield magnets 300 MHz instrument in Al-Bait University/Jorden using DMSO-d^6 as a solvent.

Synthesis of [2-chloro-N-p-tolylacetamide] (1) [16]

(0.1 mole) of p-amino toluene and (120 ml) of benzene were shaken in magnetic stirrer for (1:30) hrs. (0.1 mole) of chloro acetyl chloride was added drop wise to the pervious mixture. The mixture then stirred for 1hr., and then it was refluxed for 2hrs. The mixture was then poured into ice cold water, the obtained product was filtered and recrystallized from ethano, Table (1).

Synthesis of [2-hydrazinyl-N-p-tolythiazole-4-amine] (2) [16]

A mixture of (0.01 mole) of compound (1) and (0.01 mole) of thiosemicarbazide was dissolved in (30 ml) of ethanol. The mixture was refluxed for (6) hrs. The solid product was filtered and recrystallized from ethanol, Table 1.

Synthesis of [2-hydrazinyl-N-p-tolyloxazole-4-amine] (3) [16]

A mixture of (0.01 mole) of compound (1) and (0.01 mole) of semicarbazide was dissolved in (30 ml) of ethanol. The mixture was refluxed for (6) hrs. The solid product was filtered and recrystallized from ethanol, Table (1).

Synthesis of [N-p-tolylthiazole-2,4-diamine] (4) [16]

A mixture of (0.01 mole) of compound (1) and (0.01 mole) of thiourea was dissolved in (30 ml) of ethanol.

The mixture was refluxed for (6) hrs. The solid product was filtered and recrystallized from ethanol, Table 1.

Synthesis of Schiff Bases (5-13), General Procedure:
(0.01 mole) of each one of compounds (2, 3, and 4) and (0.01 mole) of appropriate aromatic aldehydes or ketones was dissolved in (30 ml) of ethanol, and then refluxed for (6) hrs. The solid product was filtered and recrystallized from ethanol, Table 1.

Synthesis of β-Lactam derivatives (14-22) [17]
(0.02 mole) of chloro acetyl chloride was added drop wise at (0-5) ^{o}C to a stirred solution of (0.01 mole) of any kind of Schiff bases (5-13), (0.02 mole) of triethyl amine and (15 ml) of dioxin, the reaction mixture was stirred for about (5-7) hrs. The mixture was then poured into ice water, and the product was recrystallized from different solvent, Table 1.

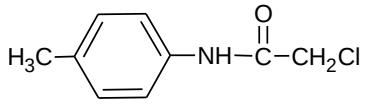
Table1:The physical properties of the prepared compounds.

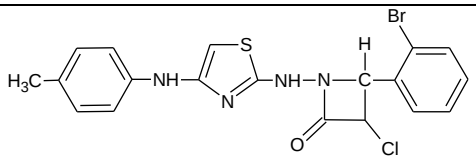
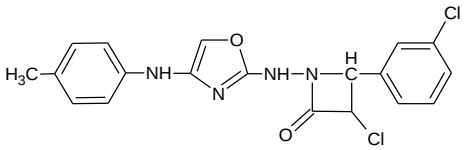
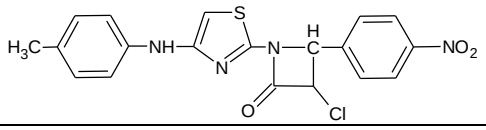
Comp. No.	Formula	**M.P. ◦C**	**Yield%**
(1)	$C_9H_{10}NOCl$	**218-219**	**79%**
(2)	$C_{10}H_{12}N_4S$	**217-219**	**70%**
(3)	$C_{10}H_{12}N_4O$	**139-140**	**68%**
(4)	$C_{10}H_{11}N_3S$	**198-200**	**79%**
(5)	$C_{17}H_{15}N_5S$	**220-221**	**60%**
(6)	$C_{17}H_{15}N_4SCl$	**223-224**	**63%**
(7)	$C_{17}H_{15}N_4SBr$	**230-232**	**64%**
(8)	$C_{17}H_{15}N_5O_3$	**215-217**	**60%**
(9)	$C_{17}H_{15}N_4OCl$	**223-224**	**55%**
(10)	$C_{17}H_{15}N_4OBr$	**210-212**	**66%**
(11)	$C_{17}H_{14}N_4O_2S$	**230-232**	**63%**
(12)	$C_{17}H_{14}N_3SCl$	**240-242**	**50%**
(13)	$C_{17}H_{14}N_3SBr$	**239-240**	**66%**
(14)	$C_{19}H_{16}N_5O_3SCl$	**200-212**	**63%**
(15)	$C_{19}H_{16}N_4OSCl_2$	**241-242**	**50%**
(16)	$C_{19}H_{16}N_4OSBr$	**235-237**	**49%**
(17)	$C_{19}H_{16}N_5O_4Cl$	**219-221**	**55%**
(18)	$C_{19}H_{16}N_4O_2Cl_2$	**231-233**	**49%**
(19)	$C_{19}H_{16}N_4O_2BrCl$	**224-226**	**50%**
(20)	$C_{19}H_{15}N_4O_3SCl$	**235-237**	**60%**
(21)	$C_{19}H_{15}N_3OCl_2$	**250-252**	**49%**
(22)	$C_{19}H_{15}N_3OBrCl$	**242-244**	**52%**

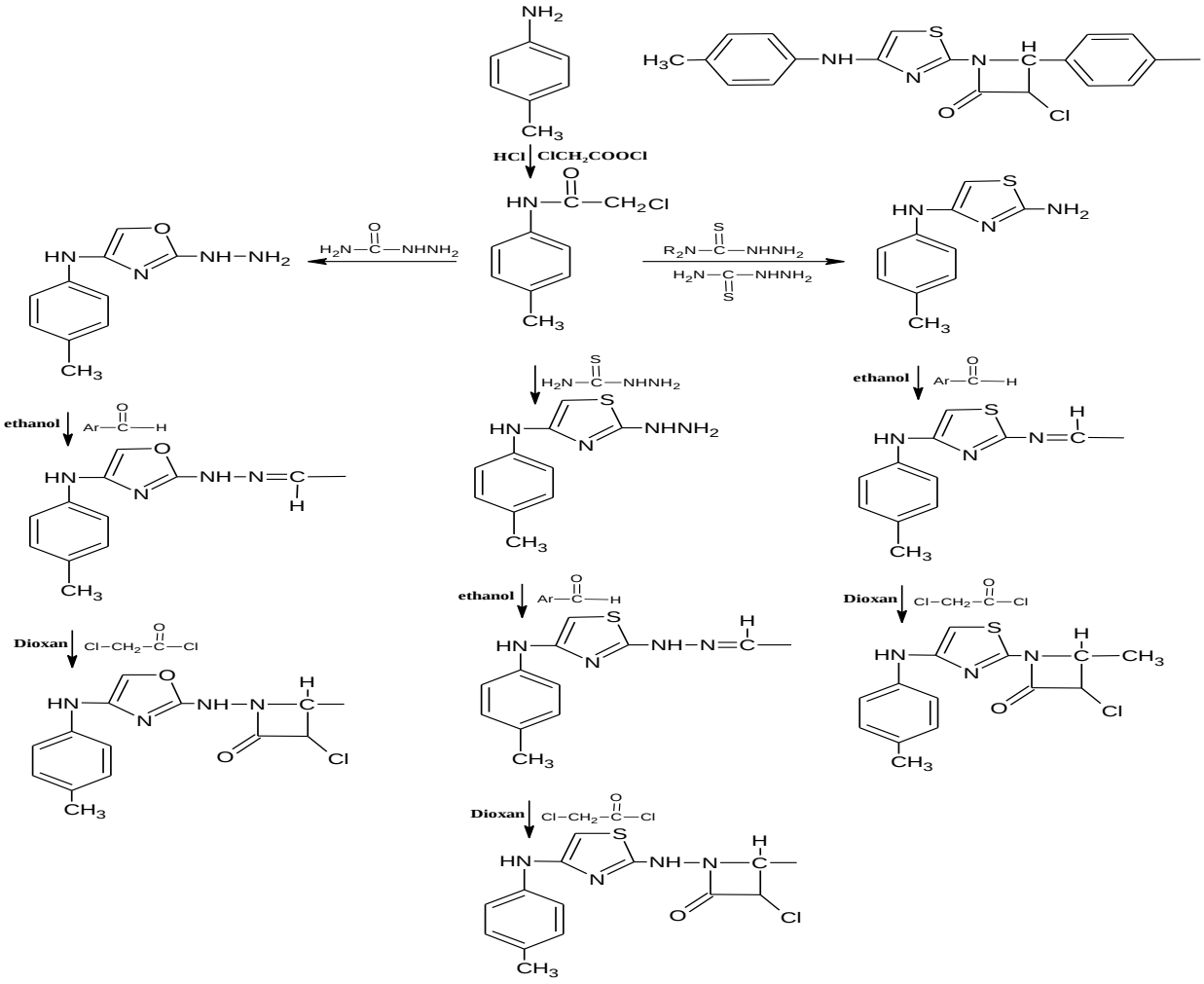
Table 2: The Physical Properties and FT-IR Spectral Data of the Prepared Compounds.

Comp. No.	**Formula**	**Infra red Data (υCm^{-1})**
(1)	$C_9H_{10}NOCl$	(N-H) 3273,(C-H)ar. 3138,(C=O) amide 1672, (C-Cl) 815, (C=C) ar. 1616
(2)	$C_{10}H_{12}N_4S$	(N-H) 3267, (C-S) 730,(CH_3) 2993, (NH_2) 3371/3171, (C=C) ar. 1616, (C=N) 1633
(3)	$C_{10}H_{12}N_4O$	(N-H)3257,(C=N)1687,(NH_2) 3309/3257, (C-O) 1388
(4)	$C_{10}H_{11}N_3S$	(N-H) 3437,(C=N) 1670,(NH_2) 3263/3201,(C-S) 730, (CH_3) 2978
(5)	$C_{17}H_{15}N_5S$	(N-H) 3417,(C=N) 1624,(NO_2sym.) 1529,(C-S) 734
(6)	$C_{17}H_{15}N_4SCl$	(NH) 3363, (C=N) 1614, (C-S) 729, (C-Cl) 891
(7)	$C_{17}H_{15}N_4SBr$	(NH)3160,(C=N)1600,(C-S)730,(C-Br) 952,(C-H) alph. 2974
(8)	$C_{17}H_{15}N_5O_3$	(NH) 3464, (C=N) 1600, (C-O) 1317, (NO_2 sym.) 1348, (NO_2asy.) 1529
(9)	$C_{17}H_{15}N_4OCl$	(NH) 3417, (C=N) 1604, (C-O) 1346, (C-Cl) 852, (CH) alph. 2989
(10)	$C_{17}H_{15}N_4OBr$	(NH) 3470, (C=N) 1658, (C-O) 1344, (C-Br) 952, (CH) alph. 2987
(11)	$C_{17}H_{14}N_4O_2S$	(NH) 3203, *C=N) 1674, (C-S) 732, (NO_2 sym.) 1352, (NO_2 asy.) 1531, (CH) alph. 2929
(12)	$C_{17}H_{14}N_3SCl$	(NH) 3203, (C=H) 1649, (C-S) 756, (CH) alph. 2976
(13)	$C_{17}H_{14}N_3SBr$	(NH) 3261, (C=N) 1649, (C-S) 756, (CH) alph. 2976, (C-Br) 916
(14)	$C_{19}H_{16}N_5O_3SCl$	(NH) 3209, (C-S) 730, (NO_2 sym.) 1305, (NO_2 asy.) 1512, (C=O) lactam 1710, (C-Cl) 891
(15)	$C_{19}H_{16}N_4OSCl_2$	(NH) 3209, (C-S) 729, (C=O) lactam 1720, (C-Cl) 891
(16)	$C_{19}H_{16}N_4OSBr$	(NH) 3100, (C-S) 730, (C=O) lactam 1722, (C-Br) 952
(17)	$C_{19}H_{16}N_5O_4Cl$	(NH) 3462,(C-O)1317,(C=O)lactam 1718,(NO_2 sym.)1348, (NO_2 asy.) 1529
(18)	$C_{19}H_{16}N_4O_2Cl_2$	(NH)3464,(C-O)1346,(C=O) lactam 1716,(C-Cl) 850
(19)	$C_{19}H_{16}N_4O_2BrCl$	(NH) 3470,(C-O) 1345,(C=O)lactam 1716,(C-Br) 952
(20)	$C_{19}H_{15}N_4O_3SCl$	(NH) 3205, (C=O) lactam 1710, (C-S) 732, (NO_2 sym.)1352, (NO_2asy.) 1529
(21)	$C_{19}H_{15}N_3OCl_2$	(NH) 3205,(C=O) lactam 1712, (C-S) 752, (C-Cl) 825
(22)	$C_{19}H_{15}N_3OBrCl$	(NH) 3206,(C=O) lactam 1714, (C-S) 756, (C-Cl) 825, (C-Br) 916

Table 3: ^{1}H.NMR Spectral Data of Some of the Prepared Compounds.

Comp. No.	Compound Structure	^{1}H.NMR Parameters 3H,(ppm) δ-H
(1)		(s,2.34,3H,CH_3),(m,6.48-7.01,4H, proton benzene ring),(s,6.28,NH), (d, 4.61, 2H,CH_2)

(16)		(s,2.43,3H CH_3),(m,6.38-7.55,4H proton benzene ring), (s, 4.7, H thiazole), (s, 2.0, NH thiazole), (s, 5.0, CH β-lactam)
(17)		(s, 2.34, CH_3), (m, 6.38-7.49,4H proton benzene ring), (s, 4.0, NH), (s, 4.7, H thiazole), (s, 5.0, H β-lactam)
(20)		(s, 2.34, 3H CH_3), (m, 6.38-8.21, 4H proton benzene ring), (s, 4.0, NH), (s, 4.7, H thiazole), (s, 5.0, H β-lactam)



Scheme1: The prepared compounds.

RESULTS AND DISCUSSION

The reaction sequence for the titled compounds is out lined in Scheme 1. Compound (1) was prepared by reaction of p-toludine with chloro acetyl chloride, the structure of compound (1) was confirmed by its FT-IR spectra through the disappearance of (NH_2) vibration and the appearance of (C=O) amide at 1672cm^{-1}. The treatment of compound (1) with thiosemicarbazide produced compound (2) 2-hydrazinyl-N-p-tolylhiazole-4-amine. Compound (2) FT-IR shows bands at 3371cm^{-1} and 3171cm^{-1} which were assigned to (NH_2) stretching vibrations and disappearance of (C=O) amide band. The treatment of compound(1) with semicarbazide produced compound (3)2-hydrazinyl-N-p-tolyloxazole-4-amine. Compound(3) FT-IR shows bands at 3307 and 3257cm^{-1} which were assigned to (NH_2) stretching vibrations and disappearance of (C=O) amide band. The treatment of compound (1) with thiourea produced compound(4)4-N-p-tolylthiazole 2,4diamine. Compound(4) FT-IR shows bands at 3263 and 3201cm^{-1} which were assigned to

(NH_2) stretching vibrations and disappearance of (C=O) amide band. Condensation of thiazole and oxazole derivative with aryl aldehydes in absolute ethanol produced Schiff bases (5-13). Formation of these Schiff bases was indicated by the presence of azommethine (C=N) stretching bands at (1600-1649)cm^{-1} combined with appearance of (NH_2) stretching band in their FT-IR spectra. Moreover treatment of Schiff bases with chloro acetyl chloride in dioxane produced β-lactam derivatives (14-22). The structure of these compounds was confirmed by the disappearance of azetidin group at (1710-1720)cm^{-1} due to (C=O) lactam.

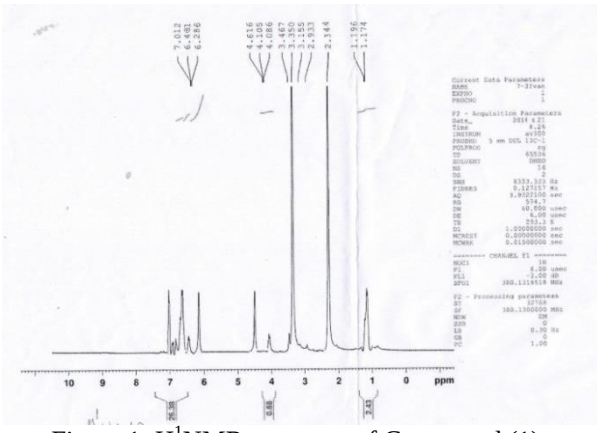


Figure 1: H^1NMR spectrum of Compound (1).

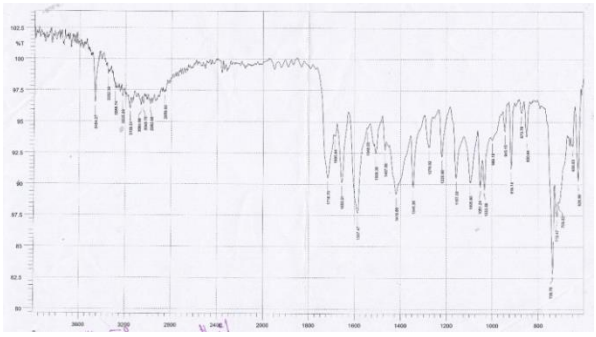


Figure 2: FTIR spectrum of Compound (16).

REFERENCES

[1] Palmer D.C.,Venkatraman S.,``The Chemistry of heterocyclic compound oxazoles: synthesis , reactions and spectroscopy`` Part A Ed., Weily & Sons, Hoboken, NJ , USA , 60:1-390, 2003.

[2] Kunieda T.,Matsunaga H.``The chemistry of heterocyclic compound, oxazoles : synthesis , reactions and spectroscopy`` Part B Ed.,Palmer D.C., Wiley & sons : Hobken , NJ, USA , 60 :1-52, 2004.

[3] Jin Z.``Imidazole,oxazole and thiazole alkoides ``Nat.Prod.Rep., 23:364-496, 2006.

[4] Yeh VSC ``Recent advances in the total synthesis of oxazole containing natural product`` Tetrahedron,60:11995-12042, 2004.

[5] Rawal RK, Tripathi R,Katti SB,Panne Couque C, De Clercq and E.Design``Synthesis and evaluation of 2-aryl-3- hetero aryl-1,3-thiazolidine-4-ones as anti-HIV agents.Bioorg.Med.Chem.;15(4):1725-31, 2007.

[6] Dabholkar Vijoy V.;Sayad S.Ahmed.,Ind.J. of heterocyclic Chem.20:171-172, 2010.

[7] Beale J. M., Block J.H., Wilson`s and Gisvold`s Textbook of Organic Medicinal and pharmaceutical Chemistry,12th Ed. ,Lippincott , Williams and Wilkins, Philadelphia,281:324-349, 2011.

[8] Shai A.A., Raghuwanshi M.G., Khurshid I., Molvi Sayyed Nazim and Aeyaz Ahmed ``Schiff`s Bases and Amides of Selected Five Membered Heterocyclic compounds`` J. Chem. Pharm. Res.,5(6):14-25, 2013.

[9] Chu D.T.W., Plattner J.J. and Kat Z.`` New Direction in Antibacterial Research`` J.Med.Chem., 39:3853,1996.

[10] Southgate R.,Contemp.Org.Synth.,1:417, 1994.

[11] De Kimpe N.``In comprehensive heterocyclic chemistry II, `` Padwa A., Ed., Elsevier: Oxford, UK, 536, 1996.

[12] Burnett D.A.,Caplen,M.A.,Davis,H.R.Jr.Burrie,R.e. & Clader J.W. ``2-Azeto -nes as Inhibitors and Cholestrol Absorption ``J.Med. Chem. 37:1733, 1994.

[13] Han W. T., Trehan a. K., wright J. j., Federici M.E.Seilder S.M. and Meanwell N.A.``Azetidin-2-one Derivatives as Inhibitors of Thrombin`` Bio.Org. Med. Chem., 3:1123, 1995.

[14] Smith D.M.,Kazi A.,Smith L.,Long T.E.,Helderth B.,Turos E.and Dou Q.P.``Novel β-Lactam Antibiotic ActivatesTumer Cell Apoptotic program by Inducing DNA Damage`` Mol. Pharmacol., 61:1348, 2002.

[15] Shah S/H.Patel P.S.``Synthesis and Antimicrobial Activity of Azetidin-2-One Containing Pyrazoline Derivatives``Res.J.Chem.Sci.,2(7)62, 2012.

[16] Ram S. Prasad,Sara Swathy T., Niraimathi V., Indhumathi B. ``Synthesis, Characterization and Antimicrobial Activity of Some of the Benzocaine Derivatives`` Int.J.Pharm. Sci. 4(5):285-287, 2012.

[17] Mada S.,Arora R.,Venago Opalan P.,Ban S.S.``Tetrahedron``Lett.,41:5577, 2000.