Heterocyclic Letters
Vol. 12| No.2|329-338|February -April|2022
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ONE-POT THREE-COMPONENT SYNTHESIS OF CHROMENO[4,3-C] PYRAZOL CARBOTHIOAMIDE AND CHROMENO[4,3,2-CD]INDAZOL CARBOTHIOAMIDE DERIVATIVES USING PIPERIDINES AS AN EFFICIENT CATALYST

Malika Leguil[1*], Mokhtar Boualem Lahrech [1*], Lahcene Souli[1] and Mokhtar Benalia[2]

[1]Laboratory of Organic Chemistry and Natural Substances, Faculty of Exact Sciences and informatics, Ziane Achour University-Djelfa, Algeria.
[2]Laboratory of Process Engineering,Departement Process Engineernig, Amar Telidgi University-Laghouat, Algeria.
**Corresponding Author. E-mail: lahrechmokhtarboualem@yahoo.fr*
**Corresponding Author. E-mail:leguilmalika@yahoo.com*

ABSTRACT

A green, efficient, and rapid procedure for the one-pot synthesis of novel chromeno[4,3-c]pyrazole carbotioamide and chromeno[4,3 ,2-cd]indazole-1- derivatives from salicylaldehyde, 1,3-dicarbonyl compounds and 2-aminobenzimidazole, under reflux conditions catalyzed by piperidine in acetic acid.The reactions are realized in short time (12h) giving an excellent yield (55-98%).The novel synthesized chromeno[4,3-c]pyrazole carbotioamide and chromeno[4,3 ,2-cd]indazole-1- derivatives were characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques.

KEYWORDS

Chromeno[4,3-c] pyrazole carbotioamide, chromeno[4,3 ,2-*cd*]indazole-1- carbothioamide ,One Pot three compounds reactions, 1,3-dicarbonyl compounds, thiosemicarbazide.

INTRODUCTION

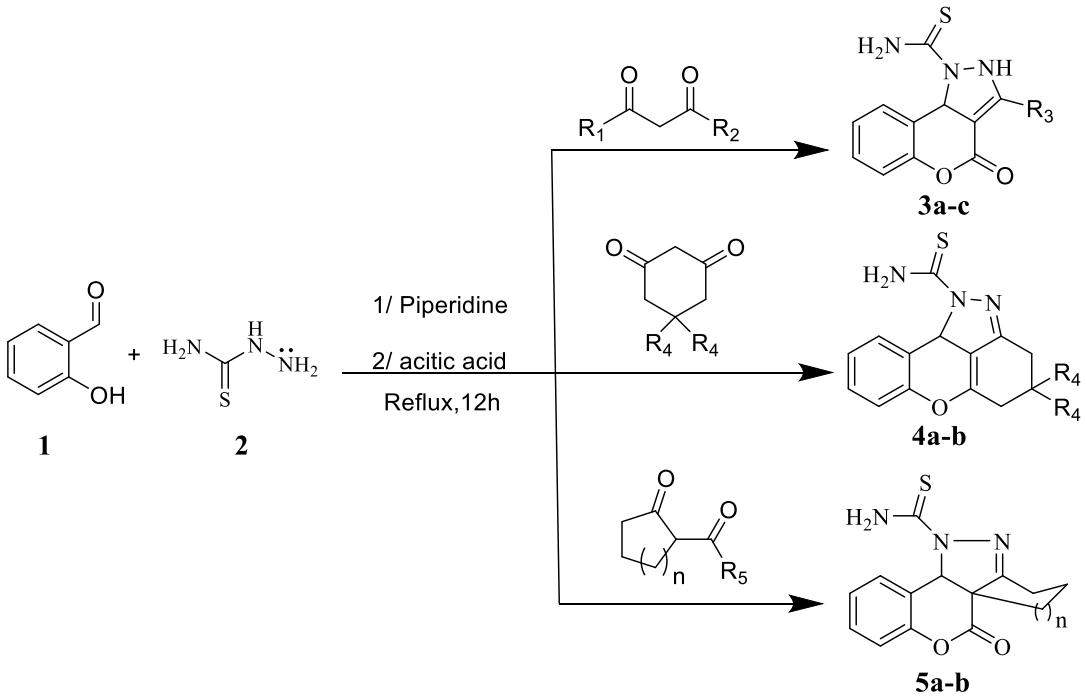
Multicomponentreactions (MCRs) represent powerfultools for construction of structurally diverse scaffolds. Through MCRs, three or more simple starting materials could react in a programmed and domino fashion to install the structurally complex products in a one-pot process[i]**.** The use of three or more reactants in a multicomponent reaction leads to a great structural and functional diversity of organic compounds. The development of new MCRs is an intellectual challenge because it is necessary to consider not only the play of reactivity of raw materials but also the reactivity of intermediate molecules generated in situ, their mutual compatibility and their compartmentalization [ii].

Chromenes derivatives represent an important heterocyclic compounds with a wide spectrum of biological and pharmacological activities. Ant-microbial[iii], anti-bacterial[iv], antiviral[v],hypotensive local anesthetic, and antiarrhythmic[vi]. mutagenicity [vii], antiproliferative

[viii], anticancer[ix] anti-inflammatory[x], antihistaminic activities [xi] fused chromene ring systems have platelet anti aggregating. Local anesthetic [xii-xiv]**.** They also act as CNS agents[xv] antioxidants[xvi]. Anticoagulant, smasmolytic,diuretic[xvii] Molluscidial[xviii]**,**inhibitory effect on inflluenza virus sialidases [xix]. They are also useful in preparing pheromones[xx]and anti tumor agents [xxi].Some of these compounds are employed in making cosmetics, pigments[xxii] and potential biodegradable agrochemi-cals[xxiii].

In particular, pyrazole derivatives have a long history of application in the pharmaceutical industry[xxiv] as part of biologically active pharmaceuticals[xxv,xxvi]**.** The activities exhibited by them include, selective COX-II inhibitor, as versatile pharmacophore of variety of biologically active heterocycles[xxvii], potential antiviral [xxviii], antimalarial[xxix], antitumor agents [xxx], as non benzodiazepine anxiolytics [xxxi, xxxii], HIV-reverse transcriptase inhibitors[xxxiii]**,** andherbicides [xxxiv]**.**

As part of our continuing efforts on the development of new routes for the synthesis of heterocyclic compounds[xxxv-xxxvii], in this work, we wish to report an one-pot chemo-selective synthesis of some new chromeno [4,3-c] pyrazol carbothioamide and chromeno[4,3,2-cd]indazol carbothioamide derivatives via reaction of salicyl aldehyde (1) with 1, 3-dicarbonyl compounds (3) and thiosemicarbazide (2), in the presence of catalytic amounts of piperidine in acetic acid.



Scheme 1: One pot reaction of three components.

EXPERIMENTAL

Materials

Melting points were measured using Kofler bench method. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm. IR spectra were recorded on a Perkin-Elmer spectrometer.^{1}H and ^{13}C NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 300 and 75MHz, respectively, in DMSO-d_6 and $CDCl_3$ Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0ppm) as an internal reference and the following multiplicity abbreviations were used: s, singlet; d, doublet;

t, triplet; q, quadruplet; m, multiplet. All chemicals products were obtained from Merck and were used without further purification.

General procedure for Synthesis of chromeno[4,3-c] pyrazol carbothioamide and chromeno[4,3,2-cd]indazol carbothioamide derivatives :

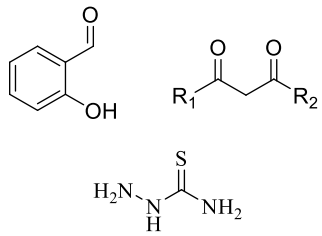
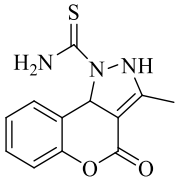
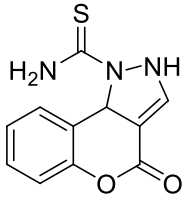
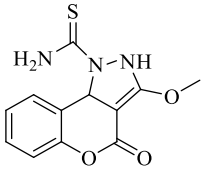
To a mixture of salicyl aldehyde (1) (1mmol), 1,3-dicarbonyl compounds (3) (1mmol, g) and thiosemicarbazide (2) (1mmol), in acetic acid is added two drops of piperidine , the mixture was heated at reflux for 12hours. Upon completion of the reaction, [monitored by TLC (eluent system: petroleum ether/ethyl acetate, 98:2)], the mixture was cooled at room temperature, the precipitated product was filtered, washed three times with ethanol, and dried at 60-70°C.

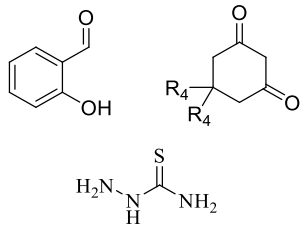
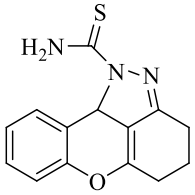
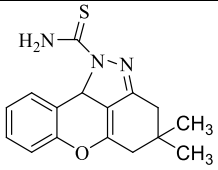
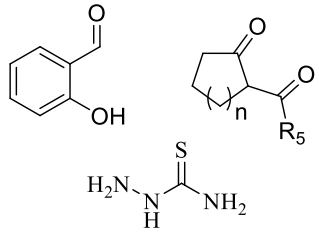
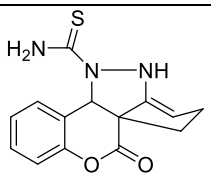
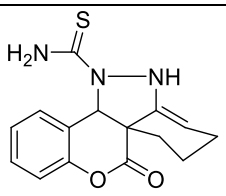
RESULTS AND DISCUSSION

We found that combining salicylaldehyde (1) with 1, 3-dicarbonyl compounds (3) and thiosemicarbazide (2) leads to the formation of chromeno[4,3-c] pyrazol carbothioamide and chromeno[4,3,2-cd]indazol carbothioamide derivatives (Scheme 1).

Generally, the polyheterocyclic compounds were obtained with good yields when mixtures of three starting components and two drops of piperidine are refluxed in acetic acid for 12 h (Table 1). The desired products precipitate upon cooling of the reaction mixture and a filtration provides analytically pure material (>95%).

Table 1: One pot synthesis of chromeno [4,3-c] pyrazol carbothioamide and chromeno [4,3,2-cd] indazol carbothioamide derivatives catalyzed by piperidine at reflux during 12h.

Entry	Réactants		Product	Yield(%)	Pm (°C)
1		$R_1 = CH_3$ $R_2 = OCH_2CH_3$	 **3a**	83	246-248
2		$R_1 = OCH_3$ $R_2 = CH_2CO_2CH_3$	 **3b**	65	248
3		$R_1 = R_2 = OCH_3$	 **3c**	98	250

4		R_4=H	 **4a**	61	260
5		R_4=CH_3	 **4b**	55	198-200
6		n=1 R_5=OCH_3	 **5a**	89	242-244
7		n = 2 R_5= O C_2H_5	 **5b**	85	244-246

Characterization

FT-IR spectroscopic analysis

The FT-IR spectrums of all obtained products have two wide bands observed between 3500-3400 cm^{-1} due to the N-Hstretching, and a strong band observed between 1598-1701cm^{-1} due to the of N-H deformation. The group (C=S) of all products is observed between 1200-1050cm^{-1}.The carbonyl groups (C=O) band of some products (**3a-c**) and (**5a-b**) is observed between 1747 and 1653cm^{-1}.The peaks associated to H-C= (aromatic) of all synthesized products were observed between 3026-3228cm^{-1} and anotherbands of C=C (aromatic) were observed about 1635cm^{-1}. The C–H symmetric and asymmetric stretching due to the (-CH_3) of some products were observed around 2957cm^{-1}.Weak bands at 1100 cm^{-1} appeared in the spectra of all synthesized products due to the ether group (C-O).

^{1}H-NMR and ^{13}C NMR spectroscopic analysis

In the ^{1}H-NMR spectra of all obtained products show a singlet between 9.85-8.38 ppm due to the proton resonance of N-H. In additionthe protons of all aromatic cycles show a multiplets in the region of δ6.81-6.89 ppm. The spectral data from FTIR, ^{1}H-NMR and ^{13}C-NMR confirmed the structure of thechromeno[4,3-c] pyrazol carbothioamide derivatives, the chromeno [4,3-c] indazole carbothioamide derivativesandchromeno [4,3‑cd]indazole carbothioamide derivatives.

Spectroscopic Data

Data for :3-methyl-4-oxo-2,9b-dihydrochromeno[4,3-c]pyrazole-1(4H)-carbothioamide (**3a**) :white powder, (mp. 246C°-248C°), IR (KBr in cm^{-1}),3300(NH),3500(NH_2),1625 (C=O), 1525(C=C),1300(C=S).
^{1}H NMR (300 MHz, DMSO))δ: 9, 85(2H, s, NH_2),δ: 8, 38(1H, s, NH),δ: 6.81-6.89 (2H, m, H Ar), δ: 6, 95-7.22 (2H, m, H Ar), 1.23 (3H, s, CH_3).
^{13}C NMR (75MHz, DMSO) 116.52, 119.75, 120.79, 127.27, 131.56, 140.23, 156.87 (CO), 178.18(CS)

Data for:4-oxo-2,9b-dihydrochromeno [4,3-c]pyrazole-1(4H)-carbothioamide(**3b**) :
(3b): yellow powder, (mp. 248°C), IR (KBr in cm^{-1}), 3300(NH),3490(NH_2),1625(C=O), 1520(C=C),1320(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,85(2H, s, NH_2), δ : 8,38(1H, s, NH),δ : 7,24-7.28 (2H, m, H Ar), δ : 6,82-6.88 (2H, m, H Ar), δ : 5,75(1H, s, CH),δ : 7.90 (1H, d, H).
^{13}C NMR (75MHz, DMSO) 116.52, 119.74, 120.81, 127.26, 131.54, 140.20, 156.87 (CO), 178.19(CS).

Data for: 3-methoxy-4-oxo-2,9b-dihydrochromeno [4,3-c]pyrazole-1(4H)-carbothioamide(**3c**): yellow powder, (mp. 250°C), IR (KBr in cm^{-1}), 3300(NH),3480(NH_2),1625 (C=O), 1530 (C=C),1400(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,86(2H, s, NH_2), δ : 8,40(1H, s, NH), δ : 6.81-6.90 (2H, m, H Ar), δ : 7,15-7.23 (2H, m, H Ar), 5.73 (1H, s,CH), 2.09 (3H, s, O-CH_3).
^{13}C NMR (75MHz, DMSO) 31.59, 55.25, 116.01, 119.47, 121.20, 126.91, 131.57, 139.86, 140.70, 157.02 (CO), 178.57(CS).

Data for: 3, 4, 5, 10b-tetrahydro-1H-chromeno [4, 3, 2-cd] indazole-1-carbothioamide (**4a**): light green powder, (mp. 260°C), IR (KBr in cm^{-1}),3300(NH_2),1625(C=N), 1500(C=C),1375(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,96(2H, s, NH_2), δ : 9,49(1H, s, NH), δ: 6.58-6.68 (2H, m, H Ar),δ: 6,90-6.94 (2H, m, H Ar), δ: 5,94(1H, s, CH), δ: 0.99(2H, t,CH_2), δ: 2,05-2.58(2H,m,CH_2).
^{13}C NMR (75MHz, DMSO):24.08 27.79, 30.94, 56.38, 111.39, 120.89, 121.36, 127.32, 130.26, 143.99, 147.72, 152.70, 157.03(CO), 178.05(CS).

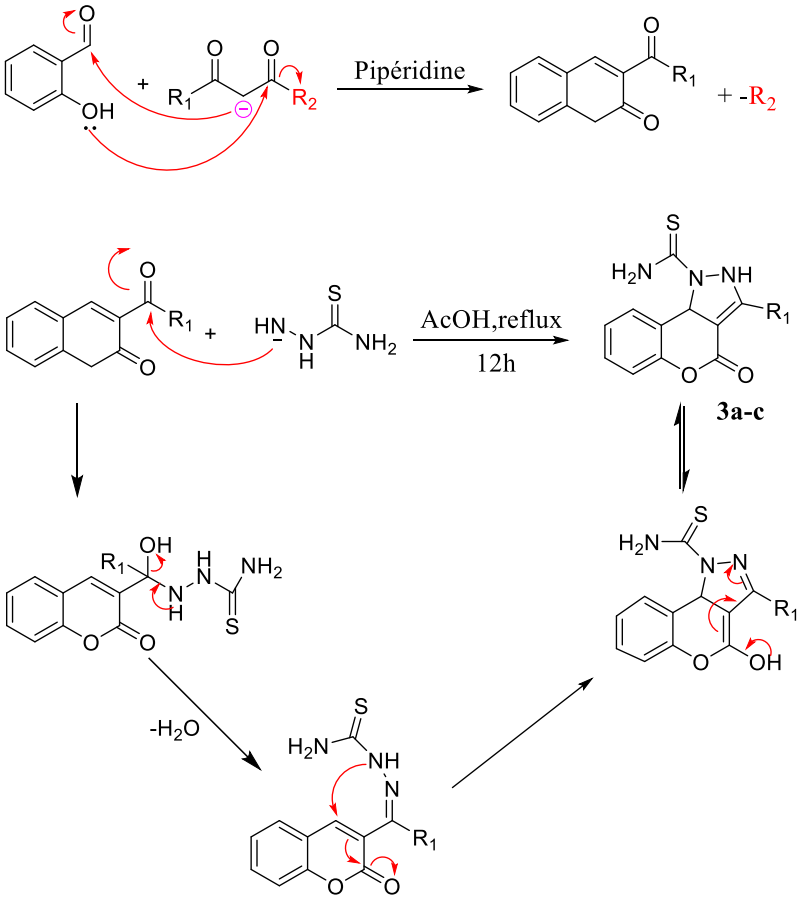
Data for: 4, 4-dimethyl-3, 4, 5, 10b-tetrahydro-1H-chromeno [4, 3, 2-cd] indazole-1-carbothioamide (**4b**): orange powder, (mp. 198°C-200°C), IR (KBr in cm^{-1}),3290(NH_2),1625(C=N), 1500(C=C),1375(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,11(2H, s, NH_2), δ : 8,37(1H, s, NH), δ: 6.85-7.21 (4H, m, H Ar), δ: 5,74(1H, s, CH), δ: 2,08 (2H,s,CH_2), δ: 0.98(6H, s,CH_3).
^{13}C NMR (75MHz, DMSO)26.84, 29.64, 32.06, 50.92, 56.89, 111.41, 119.73, 124.62, 127.31, 127.79, 138.14, 138.97, 150.17, 156.21(CO), 165.30(CS).

Data for: (5aR)-6-oxo-4,5-dihydro-2H, 6H-chromeno [4,3-c]cyclopenta[d]pyrazole-1(11bH)-carbothioamide (**5a**): brouwn powder, (mp. 242°C-244°C), IR (KBr in cm^{-1}),3295(NH),3490(NH_2),1610(C=O), 1505(C=C),1370(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,85(2H, s, NH_2), δ : 8,38(1H, s, NH), δ: 6.58-6.84 (2H, m, H Ar), δ: 7,13-7.22(2H, m, H Ar), δ: 5,75(1H, s, CH), δ: 1,09(2H, t,CH_2), δ: 2,1(2H,m , CH_2), δ: 3,35(1H, t,H vinylique)

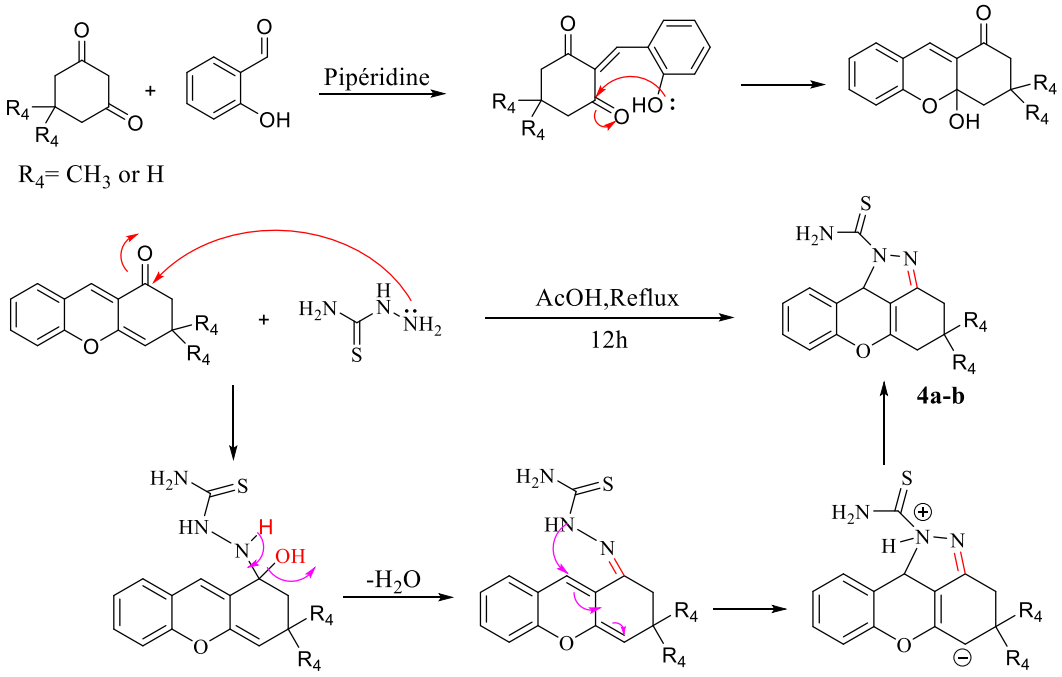
^{13}C NMR (75MHz, DMSO) 90.4, 97, 116.82, 119.48, 120.89, 126.92, 131.21, 140.20, 157.03(CO), 178.05(CS).

Data for: (6aR)-7-oxo-2, 4, 5, 6-tetrahydro-7H-chromeno [4, 3-c] indazole-1(12bH)-carbothioamide(**5b**): yellow powder, (mp. 244°C-246°C), IR (KBr in cm^{-1}),3310(NH),3490(NH_2),1610(C=O), 1500(C=C),1300(C=S).
^{1}H NMR (300 MHz, DMSO) δ : 9,85(2H, s, NH_2), δ : 8,38(1H, s, NH),δ: 7,22 (2H, m, H Ar),δ: 6,86 (2H, m, H Ar), δ: 5,75(1H, s, CH), δ: 1,06 (1H, t, H vinylic), δ: 2,09(4H,m , CH_2 ,CH_2), δ: 3,35(H, ,)
^{13}C NMR (75MHz, DMSO), 116.52, 119.74, 120.81, 127.26, 131.56, 140.26, 156.87 (CO), 178.18(CS).

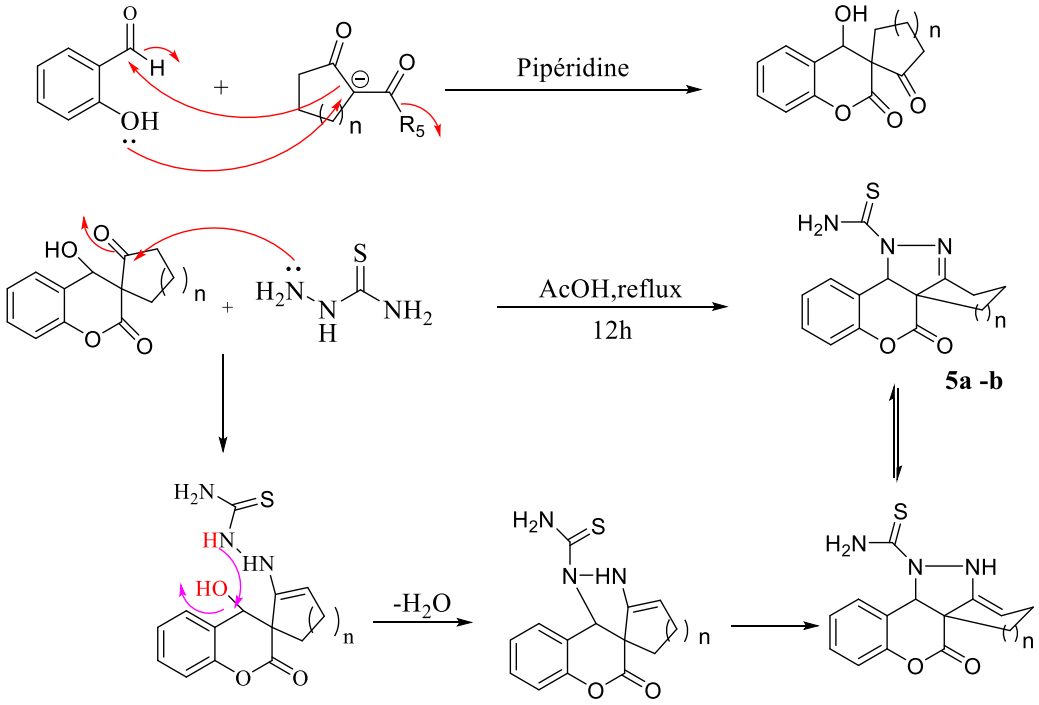
The proposed mechanism for the synthesized of chromeno[4,3-c] pyrazol carbothioamide derivatives (**3a–c**) is presented in (Scheme 2), (**4a–b**) is presented in (Scheme 3) and (**5a –b**) is presented in (Scheme 4). The mechanistic path, which we propose for this transformation, is based on the in situ formation of 3-alkyl coumarin derivative and subsequent condensation with thiosemicarbazide.



Scheme 02: Mechamism of the synthesis of chromeno[4,3-c] pyrazol carbothioamide derivatives



Scheme 03 : Mechamism for the synthesis of chromeno [4,3-c] indazole carbothioamide derivatives



Scheme 04: Mechamism for the synthesis of chromeno[4,3-c] pyrazol carbothioamide and chromeno [4,3,2-cd]indazole carbothioamidederivatives

CONCLUSION

In conclusion, the described one-pot three-component reaction of salicylic aldehyde with 1,3-dicarbonyl derivatives compounds and thiosemicarbazide in the presence of catalytic amounts of piperidine in acetic acid is an extremely efficient and chemo selective method for the synthesis of chromeno[4,3-c]pyrazol carbothioamide and chromeno[4,3,2-cd]indazol carbothioamide dérivatives. The products were obtained in good yield without further purification.

ACKNOWLEDGMENTS

We would like to thank the laboratory of organic chemistry and natural substances, faculty of exact sciences and computer science, Ziane Achour University of Djelfa, Algeria, as well as the Ministry of Higher Education and Scientific Research in Algeria for their financial support ofthis work.

REFERENCES.

i. Lai, X.,Che, C.,(2020). Synthesis of Chromeno[4,3-b]pyrrol-4(1H)-ones through a Multicomponent Reaction and Cyclization Strategy.*ACS Oméga*.,10(8)

ii. Djemoui, A., Leguil, M., Souli, L., Naouri, A ., Lahrech, M.B. (2015). One-pot three-component synthesis of chromeno[4,3-d]pyrimidinone derivatives. *Der. Pha Che*., 7(9).340

iii. Khafagy,M.M., El-Wahab,A.H.F., Eid, F.A., El-Agrody A.M. (2002)Synthesis of halogen derivatives of benzo[*h*]chromene and benzo[*a*]anthracene with promising antimicrobial activities.*II Farmaco.* 57. 9(9). 715

iv. Jiang,S., .Chen, Su.M.,Peng,F., Zhou,Q., Liu,T., Liu,L., Xue,W.(2020).Antibacterial Activities of Novel Dithiocarbamate-Containing 4H-Chromen-4-one Derivatives . *J Agric Food Chem*.,18 (7) 68, 5641−5647

v. **(a)**Smith,W.P., Sollis, L.S., Howes,D.P., Cherry,C.P., Starkey,D.I., Cobley,N.K., Weston,H., Scicinski, J.,Merritt, A., Whittington,A., Wyatt,P., Taylor,N., Green,D., Bethell, R., Madar,S., Fenton,R.J., Morley,P.J., Pateman,T., Beresford. A.J. (1998).Dihydropyrancarboxamides related to zanamivir: a new series of inhibitors of influenza virus sialidases. 1. Discovery, synthesis, biological activity, and structure-activity relationships of 4-guanidino- and 4-amino-4H-pyran-6-carboxamides.*J. Med. Chem*. 41. 787 ;**(b)** Martinez,A.G., Marco,L.J.(1997).Friedlnder reaction on 2-amino-3-cyano-4H-pyrans: Synthesis of derivatives of 4H-pyran[2,3-b] quinoline, new tacrine analogues.*Bioorg Med Chem Lett*.7.3165

vi. Farahani,F.C., Abdolmohammadi,S., Kojoori,R.K.,(2020).A PANI-Fe3O4@ZnO nanocomposite: a magnetically separable and applicable catalyst for the synthesis of chromeno-pyrido[d]pyrimidine derivatives.*The Royal Society of Chemistry*., 10.15614–15621

vii. Hiramoto, K.,Nasuhara,A., Michiloshi,K., Kato,T., Kikugawa,K.(1997). DNA strand-breaking activity and mutagenicity of 2, 3-dihydro-3, 5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP), a Maillard reaction product of glucose and glycine.*Mutat. Res*., 5 (12).47. 395.

viii. Dell,C.P., Smith. C.W. (1993) Antiproliferative derivatives of 4H-naphtho [1, 2-b]pyran and process for their preparation.*Chem. Abstr*.21 (4),119. 139102d.

ix. (a)Skommer,J., Wlodkowic, D.,Matto,M., Eray,M., Pelkonen.J.(2006). HA14-1, a small molecule Bcl-2 antagonist, induces apoptosis and modulates action of selected anticancer drugs in follicular lymphoma B cells.*Leukemia Res*. 30. 322 ; (b) Anderson,D.R., Hegde,S., Reinhard, E.,Gomez, L., Vernier,W.F., Lee,L., Liu,S., Sambandam,A., Snider,P.A., Masih. L. (2005).Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2).*Bioorg. Med. Chem. Lett*. 15 .1587 ; (c) Wang,J.L., Liu, D., Zhang,Z., Shan, S., Han,X., Srinvasula,S.M., Croce, C.M., Alnemeri,E.S., Huang,Z.(2000).Structure-based

discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells.*Proc. Natl. Acad. Sci.* USA 97. 7124.

x. Bansal,Y., Ratra,S., Bansal,G et al.(2009). Design and synthesis of coumarin substituted oxathiadiazolone derivatives having anti-inflammatory activity possibly through p38 MAP kinase inhibition. *J. Iran. Chem. Soc*., 6, 504.

xi. Gorlitzer, K., Dehre, A.,Engler,E.(1984).Untersuchungen an 1.3-Dicarbonyl-Verbindungen,22Mitt.3-Acyl-4-oxo-4H-[1]benzofuro[3,2-b] pyrane .*Arch Pharm Weinheim Ger* 317.526

xii. Bargagna,A.,Longobardi,M.,Mariani,E.,Schenone,P.,Marmo.E et al (1990).2H, 5H-[1]benzothiopyrano [4,3-b]pyran derivatives with platelet antiaggregating activity.*Il Farmaco* 45(4).405

xiii. Bargagna,A.,Longobardi,A.,Mariani,M.,Schenone,E.,Marmo,P.(1991).Benzo[6,7]cyclohepta[1,2-b]pyran derivatives with platelet antiaggregating and other activities.*Il Farmaco* 46.461

xiv. Bargagna,A.,Longobardi,M.,Mariani,E.,Schenone,P.,FFalzarano,C.(1992).Cyclohepta[b]pyran derivatives with platelet antiaggregating and other activities*Il Farmaco* 47 (3)345

xv. Eiden, F., Denk, F.,Arch. (1991).Synthesis of CNS-activity of pyran derivatives: 6,8-dioxabicyclo(3,2,1)octane*Pharm. Weinhein Ger*. (Arch. Pharm.) 324.875

xvi. Pietta,P.G., Flavonoids as antioxidants. *J. Nat. Prod*63(7).1035

xvii. Sankappa rai, U., Isloor,A.M., Shetty,P., Vijech,A.M. (2010). Novel chromeno[2,3-b]-pyrimidine derivatives as potential anti-microbial agents.*European Journal of MedicinalChemistry*.45.2695

xviii. Abdelrazek, F.M., Metz, P., Kataeva, O.,Jager ,A.,Elmahrouky,S.F.(2007).Synthesis and Molluscicidal Activity of New Chromene and Pyrano[2,3-*c*]pyrazole Derivatives. *Archiv der pharmazie* 340 (10).543

xix. Taylor,R.N., Cleasby,A.,Singh,O.,Sharzynski, T.,Wonacott,J.A.,Smith,W.P., Sollis, L.S.,Howes,D.P., Cherry ,C.P.,Berthell,R.,Colman,P..Varghese,J .(1998). Dihydropyrancarboxamides Related to Zanamivir: A New Series of Inhibitors of Influenza Virus Sialidases. 2. Crystallographic and Molecular Modeling Study of Complexes of 4-Amino-4*H*-pyran-6-carboxamides and Sialidase from Influenza Virus Types A and B.*J.Med.Chem*.41.798

xx. Bianchi, G., Tava,A. (1987). Synthesis of (2R)-(+)-2,3-Dihydro-2,6-dimethyl-4Hpyran-4-one, a Homologue of Pheromones of a Species in the Hepialidae Family.*Agric.Biol. Chem.* 51. 2001.

xxi. Mohr,S.J., Chirigos, Fuhrman,F.S., Pryor.J.W. (1975) Pyran copolymer as an effective adjuvant to chemotherapy against a murine leukemia and solid tumor.*Cancer Res*.35(12)3750

xxii. Ellis,G.P., Weissberger, A., Taylor,E.C (Eds.). (1977).The Chemistry of Heterocyclic Compounds: Chromenes, Chromanes and Chromones, *John Wiley, New York*, pp. 11–139 (Chapter II).

xxiii. Hafez, E.A.A., Elnagdi, M.H., Elagamey, A.G.A., et al. (1987) Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]coumarin and of benzo[c]pyrano[3, 2-c]quinoline Derivatives. Heterocycles, 26, 903

xxiv. Makarov,V.A., Riabova,O.B., Granik, V.G., Dahse,H.M. Stelzner,A., Wutzler,P., Schmidtke.M. (2005) Anti-coxsackievirus B3 activity of 2-amino-3-nitropyrazolo [1,5-*a*]pyrimidines and their analog.*Bioorg. Med. Chem. Lett*. 15 .3(1) 37.

xxv. Williamson,D.S., Parratt,M.J., Bower,J.F., Moore,J.D., Richardson,C.M., Dokurno,P., Cansfield,A.d., Francis,G.L., Hebdon, R.J.,Howes.R. (2005). Structure-guided design of pyrazolo[1,5-a]pyrimidines as inhibitors of human cyclin-dependent kinase 2.*Bioorg. Med. Chem. Lett*. 15. 863.

xxvi. Potts,K.T., Husain,S., Husain,S. (1970) .1,3-Dipolar reactivity in N-acylimino-derivatives of mesoionic ring systems .*Chem. Comm*. 1360.
xxvii. Potts, K.T., Husain, S. (1971). Mesoionic compound. XIV. Mesoionic compound of the imidazole series.*J. Org. Chem*. 36 .3368.
xxviii. Smirnoff,P., Crenshaw,R.R. (1977) . Stimulation of Interferon Production in Mice and in Mouse Spleen Leukocytes by Analogues of BL-20803.*Antimicrob. Agents Ch.* 11. 571.
xxix. Stein,R.G., Biel, J.H., Singh,T.(1970) .Antimalarials. 4-Substituted 1H-pyrazolo [3,4-b]quinolines *J. Med. Chem*. 13 (1)153.
xxx. Taylor,E.C., Patel.H.H.(1992). Synthesis of pyrazolo 3,4-dpyrimidine analogues of the potent agent N-4-2-2-amino-4 3H-oxo-7H-pyrrolo 2,3-dpyrimidin-5-yl ethylbenzoyl-L-glutamic acid (LY231514).*Tetrahedron*48. 8089.
xxxi. Melani,F., Cecchi,L., Palazzino,G., Filacchioni,G., Martini,C., Pennachi,E., Lucacchini.A.(1986)Pyrazolo[4,5-c]quinolines. 2. Synthesis and specific inhibition of benzodiazepine receptor binding .*J. Med. Chem*. 29(2). 291.
xxxii. Palazzino,G., Cecchi,L., Melani,F., Colotta,V., Filacchioni,G., Martini,C., Lucacchini,A. (1987) .1,3-Diarylpyrazolo [4,5-c]- and -[5,4-c]quinolin-4-ones. 4. Synthesis and specific inhibition of benzodiazepine receptor binding.*J. Med. Chem*. 30. 1737
xxxiii. Genin,M.J., Biles,C., Keiser,B.J. Poppe, B.S.M., Swaney,S.M.; Gary,W. Yagi,T.Y., Romero,D.L.(2000).Novel 1,5-Diphenylpyrazole Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors with Enhanced Activity versus the Delavirdine-Resistant P236L Mutant : Lead Identification and SAR of 3- and 4-Substituted Derivatives.*J. Med. Chem*. 43. 1034.
xxxiv. Li,Y.X.; Wang,Y.M., Liu,B., Wang,S.H., Li,Z.M. (2005) . Synthesis and herbicidal activity of 2-alkyl (aryl)-3-methylsulfonyl (sulfinyl)pyrano- [4,3-*c*]pyrazol-4(2*H*)-ones.*Heteroatom Chem*. 16 .255.
xxxv. Saeedi, M., Heravi,M.M., Beheshtiha, Y. S ., Oskooie, H.A.(2010). One-pot three-component synthesis of the spiroacenaphthylene derivatives.*Tetrahedron*, 66. 17(7).5345
xxxvi. Heravi,M.M., Saeedi, M.,Beheshtiha,Y.S., Oskooie,H.A.(2011).One-pot synthesis of benzochromeno-pyrazole derivatives*Mol. Diversity*, 15, 239.
xxxvii. Heravi,M.M, Saeedi,M, Beheshtiha,Y.S., Oskooie.H.A (2011). One-Pot Chemoselective Synthesis of Different Pyrano-pyrazole Derivatives. *Heterocycles* 83, 535.

Received on August 26, 2021.