KINGDOM OF SAUDI ARABIA
AL-IMAM MOHAMMAD IBN SAUD ISLAMIC UNIVERSITY
COLLEGE OF SCIENCE
DEPARTMENT OF CHEMISTRY

المملكة العربية السعودية
جامعة الإمام محمد بن سعود الإسلامية
كلية العلوم
قسم الكيمياء

Environment-friendly Synthesis of Bioactive Fused Pyranoyrazoles

A graduation research project

submitted to the Department of Chemistry in partial fulfillment of the requirements for the completion of the degree of Bachelor of Science in Chemistry

By

Talal M.Dhawi

Under supervision

of

Dr. Magdi E. A. Zaki

Second Semester, May 2015

Table of Content

Abstract:

A simple, straightforward and efficient multicomponent one-pot synthesis of a pharmaceutically interesting precursor with functionalized 2-amino-3-cyano-4*H*-pyranopyrazole **8** has been achieved based on low-cost available commercially materials.

Isolated functionalized pyran reacted with acetic anhydride, and carbon acids, followed by intermolecular cyclization yielding fused pyranopyridine **10** and pyranopyrimidine **12**, **13** and **14** respectively.

Acknowledgment:

My efforts bore fruit with the successful completion of this project. However, there are many others who share the reward of this effort simply because it would never have been this good without their help. I acknowledge the cooperation, encouragement and austerity of our manager, Dr. Omar Alduaij. I extend my sincere gratitude to my father Dr. Magdi who worked on this project with me .My special thanks to my parents and family for their support and understanding and of course for bearing with me when I was all too busy with the project.

Introduction

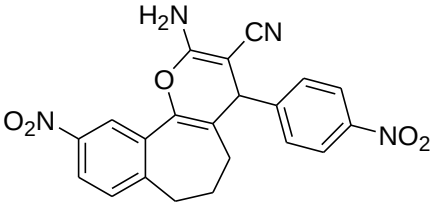
4-*H*-Pyranes and 4-*H*-pyran fused heterocyclic scaffolds represent an interesting structure distributed in naturally occurring compounds with a broad spectrum of significant biological and pharmacological activities. In the last decades, the pharmaceutical industry has actively pushed the development and achievement of greener alternatives for the exploring and synthesis of drugs and drug candidates, aiming to replace their poor atom economy reactions and polluting procedures.The present research is aiming to synthesize fused 4-*H*-pyran fused heterocyclic in greener approach and economically fruitful for pharmaceuticals.

LITERATURE REVIEWS

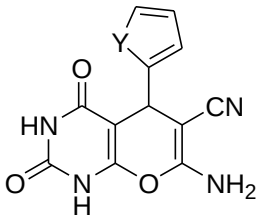
4-*H*-Pyranes and 4-*H*-pyran fused heterocyclic scaffolds represent an interesting structure distributed in naturally occurring compounds with a broad spectrum of significant biological and pharmacological activities. Multi-component reactions (MCRs) play an important role in combinatorial chemistry according to the capability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a single step from three or more reactants. Up to seven starting components have been used and producing quantitative yields than classical chemistry [1]. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions [2-4]. Ideally, all reaction equilibrium in the complex MCR mixture are reversible, and the last, product-forming reaction step is irreversible, thus prompting the driving force to shift all intermediates and starting materials towards a single final product.

The recent demands in drug discovery for more diverse small molecules and their efficient synthesis have now shifted the attention of the chemist to this as-yet largely unexplored area of chemistry. In the past few years, a variety of novel MCRs has been discovered and applied to the synthesis of biologically active molecules [5,6]. The pyranopyrazole nucleus is an interesting for biological application. Compounds containing this moiety have many pharmacological properties and play important roles in biochemical processes.

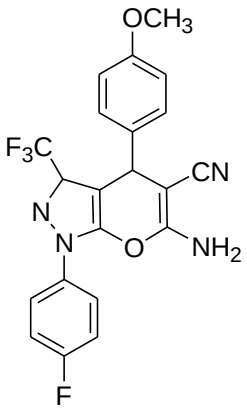
Pyrano[2,3*c*]pyrazoles have been shown as compounds with potential anticancer **A**-**C** [7], antibacterial [8a,b] antifungal [9] anti-inflammatory [10] and molluscicidal activity [11a,b], Figure 1. They have also been identified as promising human *Chk1* kinase inhibitors in computer-based screening and kinase-ihibition assays [12]



A
anticancer



B
Z= O or S, or NH
anticancer and antibacterial



C
anticancer

Figure 1

The first synthesis of 6-amino-pyrano[2,3-*c*]pyrazol-5-carbonitriles was based on the reaction of tetracyanoethylene with 3-methyl-1*H*-pyrazolin-5-one, which 4,4,5-tricarbonitrile derivatives isolated in good yields [13]. Otto had proposed the first synthesis of the dihydropyrano[2,3-*c*]-pyrazoles in 1974, via the base catalysed cycloaddition of 4-aryliden-5-pyrazolone with malononitrile.

4-aryl and alkyl substituted pyranopyrazoles [14,15] and pyranopyrazoles with spiro-annulated piperidine were reported [16,17]. The most common and simple approach toward a variety of pyranopyrazoles is a three-component base [15,17,18] of aldehydes or cyclic ketones, malonodinitrile, and corresponding pyrazolin-5-ones. This synthetic pathway gives pyranopyrazoles in high yields and can be extended to a variety of fused pyranopyrazole derivatives [19]. Another approach is based on isolation of intermediate unsaturated nitriles [18] or 4-arylidenepyrazoline-5-ones [18], known as two step protocol. Particularly, synthesis of pyrano[2,3-*c*]pyrazoles depend on reagent addition order and the order of the reaction steps in the two-step protocol, and, in the simplest variation, all starting materials can be mixed and reacted together. Exploring of new environmental friendly, more effective method for synthesis of pyranopyrazole in good yield and carrying out more reaction in water is of significant interest.

Discussion

The one-pot four component reaction of appropriate carbonyl compounds **1**, ethyl acetoacetate **2**, hydrazine hydrate **3** and malononitrile **4** was mixed together in water at room temperature in the presence of triethyl amine as a catalyst affording pyranopyrazole **8** in good yield.

Mechanistically, the reaction occurs via initial formation of *α*,*β*-unsaturated nitriles **7** by the Knoevenagel condensation between **3** and **4**, and pyrazolone **6** by the reaction between **1** and **2**, where intramolecular cyclization took place. Finally, Michael addition of pyrazolone **6** to *α*,*β*-unsaturated nitriles **7**, followed by cyclization and tautomerization yield pyranopyrazole **8,**

Figure 2.

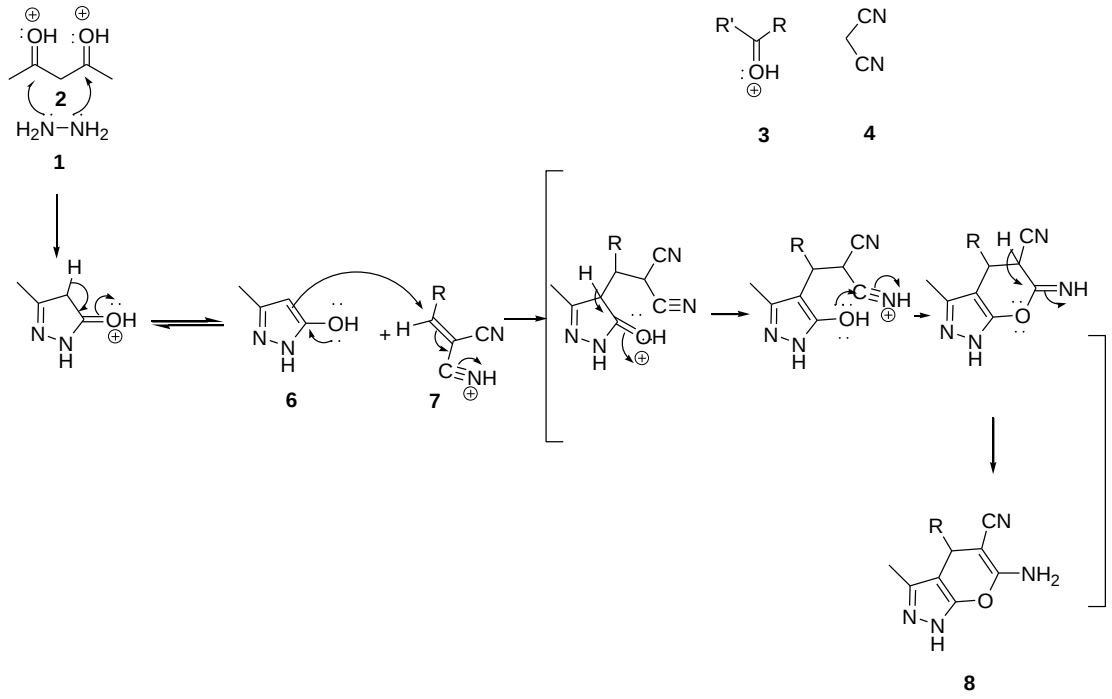


Figure 2. Proposed mechanism for Pyranopyrazole Synthesis in H_2O

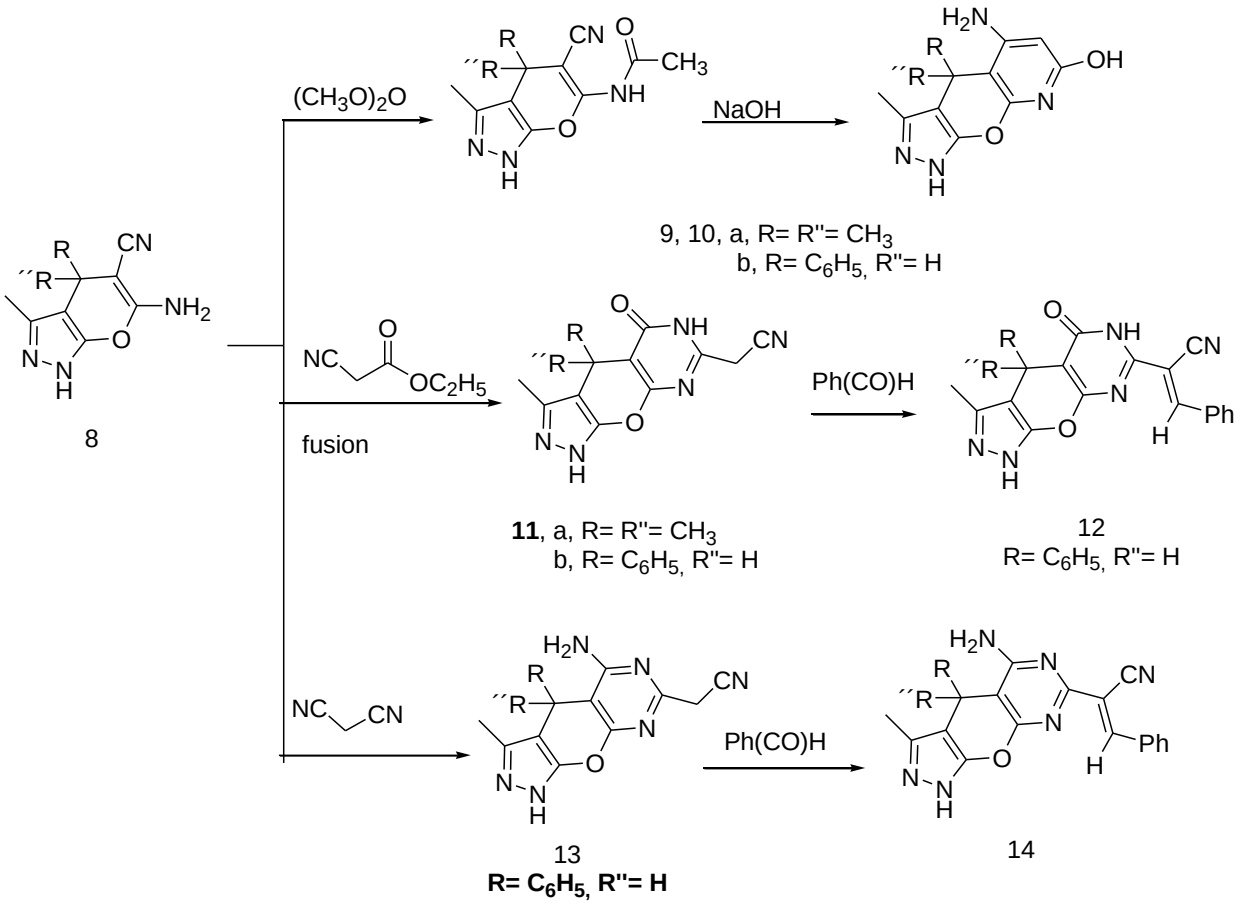
Starting from pyran moiety suitably functionalized with amino group and cyano group, we report here a simple synthesis of fused pyran moiety, pyranopyridine and pyranopyrimidine derivatives. Treatment of **8** with acetic anhydride at room temperature for 10 h yielded *N*-acetyl pyranopyrazole **9**. Scheme 1 The IR spectrum of compound **9** showed absorption bands

assignable to the NH groups, CN, and CO group. Its ^{1}HNMR spectrum showed signals at δ 2.11 (s, 3H, C3-CH_3), 2.34 (s, 3H, O=C-CH_3) ppm, 11.80, and 10.94 ppm for 2xNH (*D_2O* exchangeable).

Intramolecular cyclization took place by treating compound **9** with sodium hydroxide (2*N*) in ethanol at room temperature for 5 h. The IR spectrum of **10a** showed the disappearance of cyano group and appearance of amino group at 3310, 3220 cm^{-1}, and its ^{1}HNMR showed signals at δ6.34 ppm (s, 1H, C*H*-pyridone), 5.89- 5.79 ppm (br.s, 2H, NH_2).

Treatment pyranopyrazole **8** with ethyl cyanoacetate in absence of solvent, at fusion, afforded 2-cyanomethyl derivatives **11a,b** in good yield. An elimination of ethanol followed by intramolecular cyclization occurred. The isolated product **11a** revealed the presence of cyano group and amino group at 2227 cm^{-1} and 3323, 3245 cm^{-1} respectively. ^{1}HNMR showed signals at δ11.12 (s, 1H, NH), 10.64 (s, 1H, amidic NH) ppm, and at δ 4.47 ppm (s, 2H, CH_2) corresponding to active methylene group. The ^{13}CNMR confirmed the structure, where its spectrum revealed at δ 155.74 ppm corresponding to carbonyl amidic structure, δ110.9 ppm corresponding to the cyano group and δ24.2 ppm corresponding to active methylene group.

The presence of carbon acid analogue prompted us to react with benzaldehyde in absence of solvent, yielded the corresponding unsaturated nitriles in good yield.



Scheme 1 Synthesis of Fused Pyrazolopyran Derivatives

Continuation of our research program, the pyranopyrazole **8** reacted with malononitrile in ethanol, and in the presence of sodium hydroxide as a catalyst yielded the corresponding cyanomethyl derivatives **13** in moderate yield. Treatment of compound **13** with benzaldenhyde in ethanol, in the presence of triethyl amine as a catalyst afforded the corresponding arylidene derivative **14**.

Conclusion:

In conclusion, we have described a very simple, facile, and efficient practical method for easy access to fused 4-*H*-pyran fused heterocycles in greener approach, which have a wide range of pharmaceutically interesting heterocycles.

Experimental Part:

General:

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Deuterated DMSO was used as solvent. The chemical shifts are expressed in (ppm) and the coupling constants (*J*) in Hertz (Hz). IR spectra were recorded on a FT-IR using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel. The melting points were determined on a melting point apparatus and are uncorrected.

1- ***Synthesis of N-acetyl pyrano-pyrazole derivatives*** **(9)**

A solution of compound **8** (1mmol) in acetic anhydride (10ml) was stirred at room temperature for 10h. The formed precipitate was filtered off, dried, and recrystallized from ethanol affording **9a,b**.

1.1. ***N-(5-cyano-3,4,4-trimethyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl)acetamide*** **9a**

Yield 85%. Mp: 259-260 ^{o}C. IR (Nujol mull, cm^{-1}): 3315 (NH),3206 (NH), 2210 (CN) and 1730 (CO); ^{1}HNMR (300 MHz, DMSO-d_6, δ,ppm): 11.8 (s,1H,NH), 10.94 (s,1H, NH), 2.34(s, 3H, $COCH_3$), 2.11(s, 3H, CH_3), 1.62(s, 6H, 2X CH_3) ppm.

1.2. ***N-(5-cyano-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl)acetamide*** **9b**

Yield 89%. Mp: 276-289ºC. IR (Nujol mull, cm^{-1}): 3309 (NH), 3199 (NH), 2201 (CN) and 1724 (CO); ^{1}HNMR (300 MHz, DMSO-d_6, δ,ppm): 11.4 (s,1H,NH), 10.72 (s,1H,NH), 7.48-7.21 (m,5H, Ar), 4.48 (s,1H,*H*-pyran), 2.39, (s,3H,$COCH_3$), 1.96 (s,3H,CH_3) ppm.

2- ***Synthesis of 5-amino-pyrazolo [4`,3':5,6]pyrano[2,3-b]pyridine-7-one*** **(10)**

General procedure:

To a stirred suspention of compound **9** (20 mmol) in 2 ml water, a sodium hydroxide solution (2*N*) was gradually added over of a period 30 min. at r.t. After stirring, reflux the mixture for 2h. The reaction mixture was neutralized by adding hydrochloric acid with cooling. A white precipitate was formed, were collected by filtration, washed with water and diethyl ether several times, and dried. The isolated product identified as pyridine derivatives **10**

2.1. ***5-amino-3,4,4-trimethyl 1,4-dihydropyrazolo [4`,3`:5,6]pyrano[2,3-b]pyridine-7-ol*** **10a**

It was recrystallized from ethanol. Yield 56%. Mp: 279-280 ºC. IR (Nujol mull, cm^{-1}): 3465 (OH), 3310,3220 (NH_2), 3201 (NH); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 10.94 (s, 1H, NH), 10.24 (s,1H, NH) , 6.34 (s, H,C*H*-pyridine), 5.89-5.74 (*br*.s, 2H, NH_2) , 2.14 (s, 3H, CH_3), 1.67 (s, 6H, 2XCH_3) ppm; ^{13} C NMR (75 MHz, DMSO-d_6, δ,ppm): 155.8, 149.2,148,3, 141.7, 134.2, 107.9, 103.8, 100.4, 34.1, 30.3, 11.2 ppm.

2.2. ***5-amino-3-methyl 4-phenyl 1,4dihydro pyrazolo [4`,3`:5,6]pyrano[2,3-b]pyridine-7-one*** **10b**

It was recrystallized from ethanol**.** Yield 52%. Mp: 291-292 ºC. IR (Nujol mull, cm^{-1}):3452 (OH), 3301, 3204 (NH_2), 3191(NH)**;** ^{1}H NMR (300 MHz, DMSO-d_6, δ,ppm): 11.3 (s,1H, NH), 10.34 (s,1H,NH), 7.42-7.21 (m, 5H, Ar), 6.42 (s,1H,*CH*-pyridine), 6.24-5.92 (*br*s, 2H, NH_2) ,5.09 (s,1H, *CH*-Pyran), 2.18 (s,3H,CH_3) ppm;

3- ***Synthesis of pyranopyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-acetonitrile*** (**11**)

General procedure:

A mixture of compound **8** (1 mmol) and ethyl cyanoacetoacetate were mixed together at 120 ^{o}C For 10 min. The formed solid was collected, washed by ethanol several times and dried.

3.1. ***(3,4,4-trimethyl -5-oxo-1,4,5,6 tetrahydropyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-yl)acetonitrile*** **11a**

It was recrystallized from dimethylformamide. Yield 78%. Mp: 301-302 ^{o}C .IR (Nujol mull, cm^{-1}): 3160 (NH), 3130 (NH), 2221 (CN); ^{1}H NMR (300 MHz, DMSO-d_6, δ,ppm): 11.12 (s, 1H, NH), 10.64 (s, 1H, NH), 4.47 (s, 2H, CH_2), 1.98 (s,1H, CH_3), 1.61 (s, 6H, 2XCH_3) ppm; C^{13} NMR (75 MHz, DMSO-d_6, δ, ppm): 155.74, 148.9, 146.2, 138.7, 135.9, 110.9, 101.2, 89.4, 30.1, 28.4, 24.2, 10.1 ppm.

3.2. ***(3-methyl -5-oxo -4-phenyl 1,4,5,6- tetrahydro pyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-yl)acetonitrile*** **11b**

It was recrystallized from dimethylformamide. Yield 84%. Mp: 315-316^{o}C. IR (Nujol mull, cm^{-1}): 3169 (NH), 3140 (NH),2235 (CN); ^{1}H NMR (300 MHz, DMSO-d_6, δ,ppm): 11.31 (s, 1H, NH), 10.81 (s,1H,NH) ,7.47-7.21 (m, 5H, Ar), 4.71 (s, 1H, *H*-pyran), 4.61 (s, 2H, CH_2), 2.12 (s, 3H, CH_3) ppm; C^{13}NMR (75 MHz, DMSO-d_6, δ, ppm): 156.4, 149.2,148.1, 144.2,138.3,135.8, 129.1, 127.7, 126.3, 111.2, 102.4, 91.3, 30.1, 24.3, 11.7 ppm

4- ***(3-methyl -5-oxo -4- phenyl 1,4,5,6 tetrahydro pyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-yl)3-phenyl acetonitrile*** (**12**)

A mixture of compound **11b** (0.1 mmol) and benzaldhyde (0.11mmol) was stirred at r.t. for 3h. The formed solid was filtrated off, washed by ethanol several times, and diethylether.

It was recrystallized from dimethylformamide. Yield 69%. Mp: 332 ^{o}C. IR (Nujol mull, cm^{-1}): 3157 (NH), 3140 (NH), 2220 (CN); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 11.1 (s,1H, NH), 10.41 (s,1H, NH), 8.7 (s,1H), 7.73-7.45 (m,10H,2X Ar), 4.62 (s,1H, *H*-Pyran), 1.89 (s, 3H, CH_3)

ppm; C^{13} NMR (75 MHz, DMSO-d_6, δ, ppm): 157.1, 152.8, 150.1, 148.8, 144.9, 135.2, 132.9, 130.1, 129.7, 128.9, 129.2, 126.9, 126.2, 115.3, 102.8, 101.3, 91.7, 31.3, 11.7 ppm;

5- ***(5-Amino 3-methyl -4- phenyl-1,4,dihydropyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-yl)acetonitrile*** (**13**)

A mixture of compound **8** (1mmol) and malononitrile (0.11mmol) in a 5ml of alcoholic NaOH solution (1*N*), was refluxed for 3 h. The isolated solid was filtrated off and solublized in water followed by neutralization .The precipitate was filtrated and washed with water several times. It was recrystallized from ethanol.

Yield 73%. Mp: 328 ^oC. IR (Nujol mull, cm^{-1}): 3324, 3215 (NH_2), 3141 (NH), 2217 (CN); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 10.9 (s, 1H, NH),7.48-7.35(m, 5H, Ar) , 6.4-6.5 (*br*s, 2H, NH_2), 5.13(s,1H, *H*-Pyran), 4.51(s, 2H,CH_2), 1.93 (s, 3H, CH_3) ppm; C^{13} NMR (75 MHz, DMSO-d_6, δ, ppm): 158.1, 155.3, 152.9, 148.4, 138.6, 133.4 , 128.9, 127.1, 126.2,113.4, 93.6, 28.6, 26.2, 11.1;

6. ***(5-Amino 3-methyl -4- phenyl 1,4,dihydro pyrazolo [4`,3`:5,6]pyrano[2,3-d]pyrimidine-7-yl)3-phenyl acetonitrile*** (**14**)

The same procedure which described in preparation **12**.

Yield 69%. Mp: 328 ^oC. IR (Nujol mull, cm^{-1}): 3319, 3199 (NH_2), 3160 (NH), 2220 (CN),^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 11.1(s,1H,NH), 8.9(s,1H,CH) ,7.53-7.21 (m,10H, 2xAr), , 6.45-6.22 (*br*s, 2H, NH_2), 5.2(s,1H, H-Pyran), 1.91(s, 3H, CH_3);

References:

1. Weber, L.; Illgen, K.; Almstetter, M.; Discovery of new multi component reactions with combinatorial methods; ***Synlett****. 1999,* 3, 366– 374 and references cited in.
2. Yanlong, G.; Multicomponent reactions in unconventional solvents: state of the art, ***Green Chem***., 2012, 14, 2091.
3. Hasaninejad, A.; Zare A.; and Shekouhi M.; Catalyst-Free One-Pot Four Component Synthesis of Polysubstituted Imidazoles in Neutral Ionic Liquid 1-Butyl-3 methylimidazolium Bromide; ***J. Comb. Chem***. 2010, 12, 844, and references cited in.
4. Zolfigol M. A., Khazaei A., Moosavi-Zare A. R., Zare A. and Khakyzadeh V.; Rapid synthesis of 1-amidoalkyl-2-naphthols over sulfonic acid functionalized imidazolium salts; ***Appl. Catal.*** **A**, 2011, 400, 70.
5. Tietze, L.F.; Domino reactions in organic synthesis.; ***Chem. Rev****.19*96, 115–136.
6. Weber, L. High-diversity combinatorial libraries. ***Curr. Opin. Chem. Biol***. 2000, 4, 295–302.
7. Wang, J.; Liu, L D.; Zhang, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.;Croce, C. M.; Alnemri, E. S.; Huang, Z.*;* Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells; ***Proc. Natl. Acad. Sci. U.S.A***. 2000, *97*, 7124.
8. (**a**) Hogale, M. B.; Pawar, B. N.; An Eco-friendly Method for Novel Scaffolds: Novel N2-Substituted Fused Pyrazolo (4',3':5,6) Pyrano (2,3-d)Pyrimidine Terminated by Hydroxy Group*;* ***J. Indian Chem. Soc***. 1989, *66*,206. (**b**) Mityurina, K. V.; Kulikova, L. K.; Krasheninnikova, M. K.; Kharchenko, V. G.; New Convenient Four-Component Synthesis of 6-Amino-2,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitriles and One-Pot Synthesis of 6′-Aminospiro[(3*H*)-indol-3,4′-pyrano[2,3-*c*]pyrazol]-(1*H*)-2-on-5′-carbonitriles; ***Pharm. Chem. J.*** *(Engl.Transl.)* 1981, *15*, 861.
9. 9- Hogale, M. B.; Pawar, B. N. An Eco-friendly Method for Novel Scaffolds: Novel N2-Substituted Fused Pyrazolo (4',3':5,6) Pyrano (2,3-*d*)Pyrimidine Terminated by Hydroxy Group *;* ***J. Indian Chem. Soc***. 1989, *66*,206.
10. Zaki, M. E. A.; Soliman, H. A.;Hiekal, O. A.; Rashad, A. E.; Pyrazolopyranopyrimidines as a class of anti-inflammatory agents; ***Z. Naturforsch. (C),*** 2006, *61*, 1.

11. (**a**) Litvinov, Yu. M.; Shestopalov, A. M.; Rodinovskaya, L. A.; Shestopalov, A. A.; Fedorov, A. E. ***Proceedings of the 12-th Blue Danube Symposium on Heterocyclic Chemistry***, Tihany, Hungary, June 10-13, 2007; BDSHC-12, Book of Abstracts; ISBN: 978-963-7067-15-0. (963-7067-15-9). Chemical Research Center of Hungarian Academy of Sciences: Budapest, Hungary, 2007; PO-50. (**b**) Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F.*;* Synthesis and Molluscicidal Activity of New Chromene and Pyrano [2, 3-c] pyrazole Derivatives; ***Arch. Pharm***. 2007, *340*, 543.

12. Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor,A. E.*;* Rapid one-pot, four component synthesis of pyranopyrazoles using heteropolyacid under solvent-free condition; ***Bioorg. Med Chem***. 2006, *14*, 4792.

13. 13- Junek, H.; Aigner, H.; γ-Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in aqueous medium; ***Chem. Ber***. 1973, *106*, 914.

14. Shestopalov, A. M.; Shestopalov, A. A.; Rodinovskaya,L. A.; Multicomponent reactions of carbonyl compounds and derivatives of cyanoacetic acid: Synthesis of carbo-and heterocycles; ***Synthesis*** 2008, and reference cited in.

15. Klokol, G. V.; Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P.; New Convenient Four-Component Synthesis of 6-Amino-2,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitriles and One-Pot Synthesis of 6′-Aminospiro[(3*H*)-indol-3,4′-pyrano[2,3-*c*]pyrazol]-(1*H*)-2-on-5′-carbonitriles; ***Chem. Heterocycl. Compd. (Engl.Transl.)***; 1999, *35*, 1183–1186, and reference cited in.

16. Shestopalov, A. M.; Emeliyanova, Yu. M.; Shestopalov,, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H.; One-Step Synthesis of Substituted 6-Amino-5-cyanospiro-4-(piperidine-4‘)- 2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyrans*;* ***Org. Lett***. 2002, *4*, 423.and reference cited in.

17. Litvinov, Yu. M.; Mortikov, V. Yu.; Shestopalov, A. M.; Versatile Three-Component Procedure for Combinatorial Synthesis of 2-Aminospiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans*;* ***J. Comb. Chem***. 2008, *10*, 741, and references cited in.

18. Shestopalov, A. M.; Shestopalov, A. A.; Rodinovskaya,L. A.; Multicomponent reactions of carbonyl compounds and derivatives of cyanoacetic acid: Synthesis of carbo-and

heterocycles, ***Synthesis***, 2008,1. (**b**) Rodinovskaya, L. A.; Shestopalov, A. M.; Gromova, A. V.; Shestopalov, A. A.; ***Synthesis***, 2006, 2357, and refrences cited in.

19. Lehmann, F.; Holm, M.; Laufer, S. *J.;* Three-Component Combinatorial Synthesis of Novel Dihydropyrano[2,3-*c*]pyrazoles*;* ***J. Comb. Chem.*** 2008, *10*, 364.

CV

Name: Talal Motlaq AL Otaibe

College: College of Sciences

Department: Chemistry

University: Imam Muhammad bin Saud University

Date of Birth: 03/17/1413

Place of Birth: Dammam

E-mail: talal.alotaibe@gmail.com

Mobile: 0555975975

Phone: 0114951872

Post address: 22149

Postal Code: 24436