Synthesis of new coumarin derivatives using Diels-Alder reaction

A. Y. Soliman[1], F. K. Mohamed[1], Ramadan M. Abdel-Motaleb[1], Rasha M. Abdel-Rahman[2 (*)], A. M. Abdel-Mohsen[3,5], Moustafa M. G. Fouda [4 (*)], Salem S. Al Deyab [4], Asmaa S. Mohamed[6]

[1] Chemistry Department, Faculty of Science, Fayoum University, Fayoum, Egypt.
[2] Institute of Organic Chemistry and Technology, University of Pardubice, Czech Republic
[3] Central European Institute of Technology (CEITEC), Brno University of Technology, Brno, Czech Republic.
[4] Chemistry Department, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia.
[5] Textile Research Division, National Research Center, Dokki, Giza, P.O. 12622, Giza 12522, Egypt.
[6] Department of Medical Chemistry, Theodor Bilharz Research Institute, Egypt.
rmmar2008@yahoo.com, m_gaballa@yahoo.com, mmfoudah@ksu.edu.sa

Abstract: A novel series of new coumarin derivatives were prepared using Diels-Alder reaction. Derivatives of chromeno 2, 4- dione 1a, b reacted with dienophile such as cinnamic acid, acrylonitrole and maleic anhydride to afford Diels-Alder adduct 2-4a, b respectively. In addition, compound 4 reacted with hydrazine hydrate to afford the corresponding pyidazine derivatives 5.

[A. Y. Soliman, F. K. Mohamed, Ramadan M. Abdel-Motaleb, R. M. Abdel-Rahman, A. M. Abdel-Mohsen, Moustafa M. G. Fouda, Salem S. Al Deyab, Asmaa S. Mohamed. **Synthesis of new coumarin derivatives using Diels-Alder reaction**. *Life Sci J* 2013; 10(4):846-850] (ISSN: 1097-8135). http://www.lifesciencesite.com. 108

Keywords: Coumarin, pyrano, pyridazine and Diels-Alder.

1. Introduction

The Diels-Alder reaction is one of the most important reactions in organic synthesis [1, 2]. It is widely used in heterocyclic reaction especially for the preparation of six-member compounds [3, 4].

The chemistry of coumarins has received a great attention due to the importance of coumarins as a great class of heterocyclic compounds [5-8]. Many of biological activities have been reported for coumarins as anticoagulant, antimicrobial, antiviral and anti-inflammatory and it's widely used in the perfume, cosmetic and pharmaceutical industries [9-13]. In this research, we used derivatives of coumarin as a diene to can prepare new compounds via Diels-Alder reaction.

2. Experimental

Melting points were determined by an electro thermal melting point apparatus and are uncorrected.The reaction times were determined using the thin-layer chromatography (TLC) technique which was performed with fluorescent silica gel plates HF245 (Merck) and plates were viewed under UV 245 and 265 light. Silica gel (230-400 mesh) was used for flash chromatography separations. Elemental analysis were carried out by Micro analytical Unit, (Faculty of Science,Cairo University), IR (KBr) spectra were recorded on a Pye-Unicam infrared spectrophotometer SP 2000 (Faculty of Science, Fayoum University), The mass spectra were run by a Shimadzu-GC-MS-GP 1000 EX using the direct inlet system and Nuclear magnetic resonance spectra were recorded on Varian Mercury 300MHz spectrometer using TMS as internal standard; chemical shifts are recorded in δ units (National Center Researcher).

Synthesis of 2-carboxy-3-phenyl-4-aryl-2, 3, 4, 5-tetrahydro-pyrano [3, 2-c] chromen-5-one 2a, b

A solution of cinnamic acid (1.48g, 0.01mol.) in dioxane was added on a solution of 1a, b (0.01mol.) in dioxane and refluxed for 15hrs.The reaction mixture was concentrated and cooled. The solid product was filtered off and crystallized from propel solvent.

2a: crystallized from dioxane as a yellow crystal in 85% yield m.p.258-260 ºC. Analysis for C26H18O7 (M.wt.442.42). Calculated %: C 70.58, H 4.10, Found % C 70.62, H 4.09, IR (cm-1): 3472 due to νOH of carboxylic acid, 3015 due to νCH aromatic, 2847 due to νCH aliphatic, 1731, 1659 due to νCO of δ-lactone and carboxylic acid, MS(m/z%): 442(6.29%).

2b: crystallized from dioxane as a black crystals in 55% yield, m.p.>360 ºC. Analysis for C23H16O6 (M.Wt.388.37) Calculated % C 71.13, H 4.15, Found %:C 71.28, H 4.10, IR(cm-1): 3473 due to νOH of carboxylic acid and 3069 due to νCHaromatic, 2977 due to νCH aliphatic, broad band at 1714 due to 2νCO of δ-lactone and carboxylic acid1H-NMR (δ,ppm,DMSO-d6):3.53-5.50 (d,3H,CH),5.92 (s,2H,CH2), 6.50-7.65 (m,12H,3Ar-H), 11.20 (s,1H,OH).

Synthesis of 3-carboxy-4-aryl-3, 4, 5-trihydro-2-dihydro- pyrano [3, 2-c] chromen-5-one 3a, b.

A mixture of acrylonitrile (0.01mol.) in dioxane was added on solution of 1a (0.01mol.) indioxane and refluxed for 15hrs. The reaction mixture

was concentrated and cooled. The solid product was filtered off and crystallized from propel solvent.

3a: crystallized from dioxane to give yellow crystals in 89% yield m.p.248 ºC. Analysis for C20H14O7 (M.wt.366.07). Calculated %:C 65.57, H 3.85, Found %: C 65.30, H 3.73, IR(cm-1) 3448 due to νOH in carboxylic acid, 3088 to νCH aromatic, 2874 due to νCH aliphatic, 1731 and 1660 due to νCO of δ-lactone and carboxylic acid.

3b: crystallized form dioxane to give black crystals in 61 % yield, m. p. >360 ºC. Analysis for C17H12O6 (M.wt.312.06). Calculated %: C 65.39, H 3.87, Found %: C 65.55, H 3.61, IR(cm-1): 3456 due to νOH in carboxylic acid, 3066 to νCH aromatic, 2912 due to νCH aliphatic,1737 and 1680 due to νCO of δ-lactone and carboxylic acid.

Synthesis of 7-benzo [1, 3] dioxol-5-yl-7a,10a-dihydro-7H-5, 9, 11-trioxa-cyclopenta [b] phenanthrene-6, 8, 10-trione 4

A solution of maleic anhydride (0.98g, 0.01mol.) in dioxane was added on solution of 1a (2.94g, 0.01mol.) in dioxane and refluxed for 15hrs. The reaction mixture was concentrated and cooled. The solid product was filtered off and crystallized from propel dioxane to give yellow crystals in 88% yield m.p.248 ºC.

Analysis for $C_{21}H_{12}O_8$ (M.wt.392.32).Calculated %: C 64.29, H 3.08, Found %: C 64.32, H 3.07, IR (cm-1): 3065 due to νCH aromatic, 2914 due to νCH aliphatic, 1740,1670 νCOof δ-lactone and anhydride ring.

Synthesis of 7 a, 9, 10, 11a-tetrahydro-7H-5, 12-dioxa-9,10-diaza benzo [a] anthracene -6, 8, 11-trione derivatives 5

A mixture of compound 4 (3.92g, 0.01mol.), excess of hydrazine hydrate (98%) (3ml), few drops of piperidine in absolute ethanol was added and refluxed for 9hrs. The reaction mixture was cooled, poured into ice and hydrochloric acid.The solid product was filtered off and crystallized from ethanol as orange crystals in 54% yield,m.p.288ºC.Analysis for C21H14N2O7(M.wt.406.35). Calculated % C 62.07, H 3.47, N 6.89, Found % C 61.80, H 3.73, N 6.99, IR(cm-1): 3334, 3225 2νNH, 1710 νCO of δ-lactone and 1681,1673 νCO of amide. MS (m/z %): 406 (2.13%), 408 (2.57%).1H-NMR (δ,ppm,DMSO-d6):3.40-5.1(d,3H,CH-pyran), 5.93 (s,2H,OCH2O),6.52-7.63(m,7H,2Ar-H),8.0(s,2H,2NH).

2.1. Antibacterial activity

Coumarin and its derivatives represent one of the most active classes of compounds possess a wide spectrum of biological activity. Many of these compounds have been used for the treatment of various diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, AIDS associated dementia, and schizophrenia [14-16]. The present study reports the evaluation of the antibacterial activity of the newly synthesized compounds towards different types of Gram (+ve) and Gram (-ve) bacteria. The disc diffusion method [17] is used in this study. Compounds 2b, 3b showed excellent activity against Streptococci while compounds 2a, 3a, 4 and 5 exhibited no activity. All tested compounds showed no activity against Gram (-ve) as shown in Table 1.

2.1.1. Culture media

Muller-Hinton agar medium g/l	
Beef extract powder	**3.0**
Casein hydrolase	**17.5**
Starch	**1.5**
Agar	**17.0**

2.1.2. Preparation of agar

Muller-Hinton agar (38 g) was suspended in one liter of distilled water, then left for heating in orderto dissolve the medium completely. Later on, the medium is sterilized using autoclaving at 121 ºC for 15 min [18].

2.1.3. Test Organisms

• The Gram positive bacteria: Bacillus Subtilis and Streptococci.

• The Gram negative bacteria: Klebsiella Pneumoniae and Escherichia Coli.

2.1.4. Antibacterial test

The antimicrobial activity of each compound under investigation was evaluated in term of disc diffusion method using sterile whatman-No5 filter paper discs (11 mm diameter) [17] which explained as follow: "Each compound was dissolved in N, N-dimethylformamide (DMF). Filter paper discs (11 mm) were loaded with certain amount of the tested material (50µL), then left for complete dryness" [17]. "Then test plate were prepared by pouring 10 ml Muller-Hinton agar medium seeded with the test organism" [17]. "The discs were deposited on the surface of agar plates along with control disc, which loaded only with used solvent" [17]. The discs were incubated at 5 ºC for 1 hrs. in order to permit good diffusion. "All the plates were then incubated for 24 hrs. at 37 ºC" [17]. Finally, the inhibition zones were measured and tabulated.

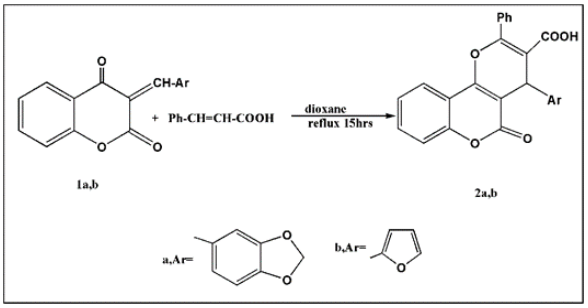
Table 1. Antibacterial activity of compounds 2 a,b, 3a,b, 4 and5.

Compound	Antibacterial activity			
	Gram +ve bacteria		Gram -ve bacteria	
	Bacillus Subtilis	*Streptococci*	*Klebsiella Pneumoniae*	*Escherichia Coli*
2a	-	-	-	-
2b	-	+++	-	-
3a	-	-	-	-
3b	-	>+++	-	-
4	-	-	-	-
5	-	-	-	-
Control	-	-	-	-

- = no activity + = weak activity
++, +++ = moderate activity >+++ = strong activity

3. Results and Discussion

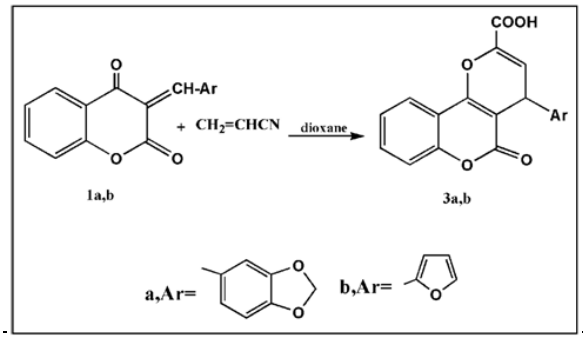
Derivatives of chromeno-2,4-dione 1a,b [19] underwent the reaction with cinnamic acid in a refluxing dioxane to yield 2-phenyl-3-carboxypyrano[3,2-c]chromene-5-one derivatives 2 a, b [18, 20].



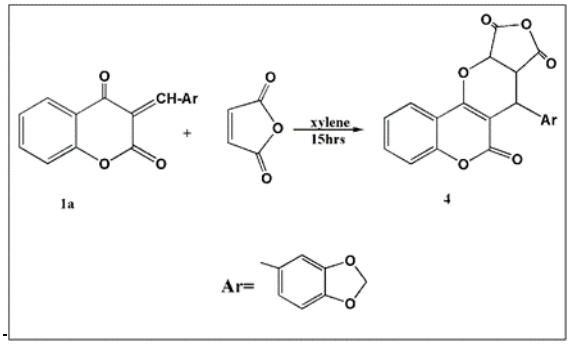
Scheme 1

The structures 2 a, b were confirmed from elemental analysis and spectral data. The IR spectrum of 2a,b showed strong absorption band at 3473-3472 cm-1due to νOH of the carboxylic group and absorption band at 1731-1714 cm-1 due to νCO of δ-lactone and at 1659 cm-1 due to νCO of carboxylic acid. The 1H-NMR (DMSO-d6) spectrum of compound 2b showed signal at δ 4.20 ppm (s,1H,CH-Ar), 5.85-7.65 ppm (m,12H,3Ar-H),11.20 ppm (s,1H,OH). The mass spectrum of compound 2a showed ion peak at m/e = 440 (6.29%) corresponding to the molecular formula $C_{26}H_{16}O_7$.

The interaction of 1 a, b with acrylonitrile in dioxin gave 2-carboxy-pyrano [3, 2-c]chromen-5-one derivatives 3 a, b via Diels-Alder reaction (Scheme 2) [21]. The structures of compounds 3 a, b were confirmed from their elemental analysis and spectral data. The CN group converts to COOH group by hydrolysis. IR spectrum showed strong absorption band at 3456-3448 cm-1 due to νOH, absorption band at 1737, 1731 and 1660 cm-1 due to νCO of δ-lactone and carboxylic group. Compound 1a reacted as a diene with maleic anhydride which act as a dienophiles in refluxing xylene for 15hrs to afford 4 (Scheme 3) [21].

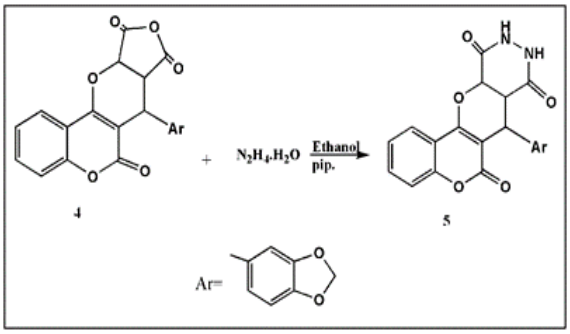


Scheme 2



Scheme 3

The structure of compound 4 was confirmed from its elemental analysis and spectral data. IR spectrum showed absorption band at 3065 cm-1due to νCH aromatic, 2914 cm-1 due to νCH aliphatic, strong absorption bands at 1740, 1670 cm-1due to νCO of δ-lactone and anhydride ring. The action of hydrazine hydrate as a nitrogen nucleophillic on compound 4 resulted in the formation of pyridazine derivative 5 [22].



Scheme 4

The structure of compound 5 was confirmed from its elemental analysis and spectral data. IR spectrum showed strong absorption band at 3334, 3225 cm-1 due to 2ν NH, absorption band at 1710 cm-1 due to νCO of δ-lactone, 1681, 1673 cm-1 due to νCO of amide. The ^{1}H-NMR(DMSO-d6) of X showed signal at δ 3.40-5.16 ppm (m,3H,CH-pyran), 5.90 ppm (s,2H,O-CH2-O), 6.52-7.63 ppm (m,7H,2Ar-H), 8.0 ppm (s,2H,2NH). The mass spectrum of compound 5 showed ion peak at m/e = 406 (2.13%) corresponding to the molecular formula $C_{21}H_{14}N_2O_7$.

4. Conclusion

A series of new coumarin derivatives were successfully synthesized using Diels-Alder reaction. All the new compounds were characterized and tested for their antibacterial activities. Some of the synthesized compounds showed excellent activity against Streptococci, while all compounds showed no activity against Gram –ve bacteria.

Acknowledgements

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research, through the research group project no. **RGP- VPP-201.**

The work was financially supported by the project "CEITEC -Central European Institute of Technology – excellent teams (CZ.1.07/2.3.00/30.0005) financed from European Social Fund.

Corresponding Author(s):

1. Dr. **Rasha M. Abdel-Rahman**
Institute of Organic Chemistry and Technology, University of Pardubice, Czech Republic.
E-mail: rmmar2008@yahoo.com

2. Dr. **Moustafa M. G. Fouda**
Chemistry Department, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia,
m_gaballa@yahoo.com, mmfoudah@ksu.edu.sa

References

[1] Khoshkholgh MJ, Lotfi M, Balalaie S, Rominger F. Efficient synthesis of pyrano[2,3-c]coumarins via intramolecular domino Knoevenagel hetero-Diels–Alder reactions. Tetrahedron. 2009;65(21):4228-34.

[2] Shanmugasundaram M, Manikandan S, Raghunathan R. High chemoselectivity in microwave accelerated intramolecular domino Knoevenagel hetero Diels–Alder reactions—an efficient synthesis of pyrano[3-2c]coumarin frameworks. Tetrahedron. 2002;58(5):997-1003.

[3] Gautam DR, Protopappas J, Fylaktakidou KC, Litinas KE, Nicolaides DN, Tsoleridis CA. Unexpected one-pot synthesis of new polycyclic coumarin[4,3-c]pyridine derivatives via a tandem hetero-Diels–Alder and 1,3-dipolar cycloaddition reaction. Tetrahedron Letters. 2009;50(4):448-51.

[4] Nair V, Jayan CN, Radhakrishnan KV, Anilkumar G, Rath NP. [4+2] Cycloaddition reactions of coumarin quinone methide with pentafulvenes: facile synthesis of novel polycyclic pyran derivatives. Tetrahedron. 2001;57(27):5807-13.

[5] Tollari S, Palmisano G, Cenini S, Cravotto G, Giovenzana GB, Penoni A. Synthesis of Furocoumarins via Rhodium(II)-Catalysed Heterocyclisation of 3-Diazobenzopyran-2,4(3H)-dione with Terminal Alkynes. Synthesis. 2001;2001(05):0735-40.

[6] Appendino G, Cravotto G, Toma L, Annunziata R, Palmisano G. The Chemistry of Coumarin Derivatives. Part VI. Diels-Alder Trapping of 3-Methylene-2,4-chromandione. A New Entry to Substituted Pyrano[3,2-c]coumarins. The Journal of Organic Chemistry. 1994;59(19):5556-64.

[7] Stanchev S, Momekov G, Jensen F, Manolov I. Synthesis, computational study and cytotoxic activity of new 4-hydroxycoumarin derivatives. European Journal of Medicinal Chemistry. 2008;43(4):694-706.

[8] Das B, Ravikanth B, Ramu R, Laxminarayana K, Rao BV. Iodine catalyzed simple and efficient synthesis of 14-aryl or alkyl-14-H-dibenzo[a,j]xanthenes. Journal of Molecular Catalysis A: Chemical. 2006;255(1–2):74-7.

[9] Refouvelet B, Guyon C, Jacquot Y, Girard C, Fein H, Bevalot F, et al. Synthesis of 4-hydroxycoumarin and 2,4-quinolinediol derivatives and evaluation of their effects on the viability of HepG2 cells and human hepatocytes culture. Eur J Med Chem. 2004;39(11):931-7.

[10] Jeong TS, Kim KS, Kim JR, Cho KH, Lee S, Lee WS. Novel 3,5-diaryl pyrazolines and pyrazole as low-density lipoprotein (LDL) oxidation inhibitor. Bioorg Med Chem Lett. 2004;14(11):2719-23.

[11] Saibara T, Toda K, Wakatsuki A, Ogawa Y, Ono M, Onishi S. Protective effect of 3-methyl-1-phenyl-2-pyrazolin-5-one, a free radical scavenger, on acute toxicity of paraquat in mice. Toxicol Lett. 2003;143(1):51-4.

[12] Shih M-H, Ke F-Y. Syntheses and evaluation of antioxidant activity of sydnonyl substituted thiazolidinone and thiazoline derivatives. Bioorganic & Medicinal Chemistry. 2004;12(17):4633-43.
[13] Stanchev S, Momekov G, Jensen F, Manolov I. Synthesis, computational study and cytotoxic activity of new 4-hydroxycoumarin derivatives. Eur J Med Chem. 2008;43(4):694-706.
[14] Okamoto T, Kobayashi T, Yoshida S. Current Medicinal Chemistry - Anti-Cancer Agents. 2005 5:47.
[15] Breckenridge AM, Cholerton S, Hart JA, Park BK, Scott AK. A study of the relationship between the pharmacokinetics and the pharmacodynamics of the 4-hydroxycoumarin anticoagulants warfarin, difenacoum and brodifacoum in the rabbit. British Journal of Pharmacology. 1985 84(1):81-91.
[16] Kok J, van Dijl JM, van der Vossen JM, Venema G. Cloning and expression of a Streptococcus cremoris proteinase in Bacillus subtilis and Streptococcus lactis. Applied and Environmental Microbiology. 1985;50(1):94-101.
[17] Difco. Laboratories Incorporated Detroit Michigan O, U.S.A, 1969.
[18] Flores-Larios IY, López-Garrido L, Martínez-Martínez FJ, González J, García-Báez EV, Cruz A, et al. Thermal [4 + 2] Cycloadditions of 3-Acetyl-, 3-Carbamoyl-, and 3-Ethoxycarbonyl-Coumarins with 2,3-Dimethyl-1,3-butadiene under Solventless Conditions: A Structural Study. Molecules. 2010;15(3):1513-30.
[19] Svetlik J, Hanus V, Bella J. Expedient Synthesis of 3-Arylpropionic Acid Derivatives. Synthetic Communications. 1993;23(5):631-40.
[20] Cravotto G, Nano GM, Palmisano G, Tagliapietra S. An asymmetric approach to coumarin anticoagulants via hetero-Diels–Alder cycloaddition. Tetrahedron: Asymmetry. 2001;12(5):707-9.
[21] Kailas K. S., Shriniwas D. S. Synthesis of fluorescent dibenzopyranones by the Diels-Alder reaction of 4-styrylcoumarins and N-phenylmaleimide and in situ aromatization using DDQ. ARKIVOC. 2013;3:109-18.
[22] Mohammed FK, Essawy AI, Badrey MG. Facile and Convenient Synthesis of Novel Benzopyranopyrimidine Derivatives Asian Journal of Chemistry 2009;21(8):5873-87

20/11/2013