Molecules **2003**, *8*, 541-555

molecules

ISSN 1420-3049

http://www.mdpi.org/

Microwave Assisted Synthesis, Part 1: Rapid Solventless Synthesis of 3-Substituted Coumarins and Benzocoumarins by Microwave Irradiation of the Corresponding Enaminones.

Khadijah M. Al-Zaydi*

Department of Chemistry, Girl's College of Education, Jeddah, P.O.50918 Jeddah 21533, Kingdom of Saudi Arabia

* Author to whom correspondence should be addressed; e-mail eman@cyberia.net.sa

Received: 18 March 2003; in revised form: 15 June 2003 / Accepted: 20 June 2003 / Published: 15 July 2003

Abstract: The reactivity of enaminones toward a variety of reagents under microwave irradiation is reported. The results are compared with traditional solution methods.

Keywords: Enaminones, coumarins, benzocoumarins, Nenitzescu reaction, microwave irradiation.

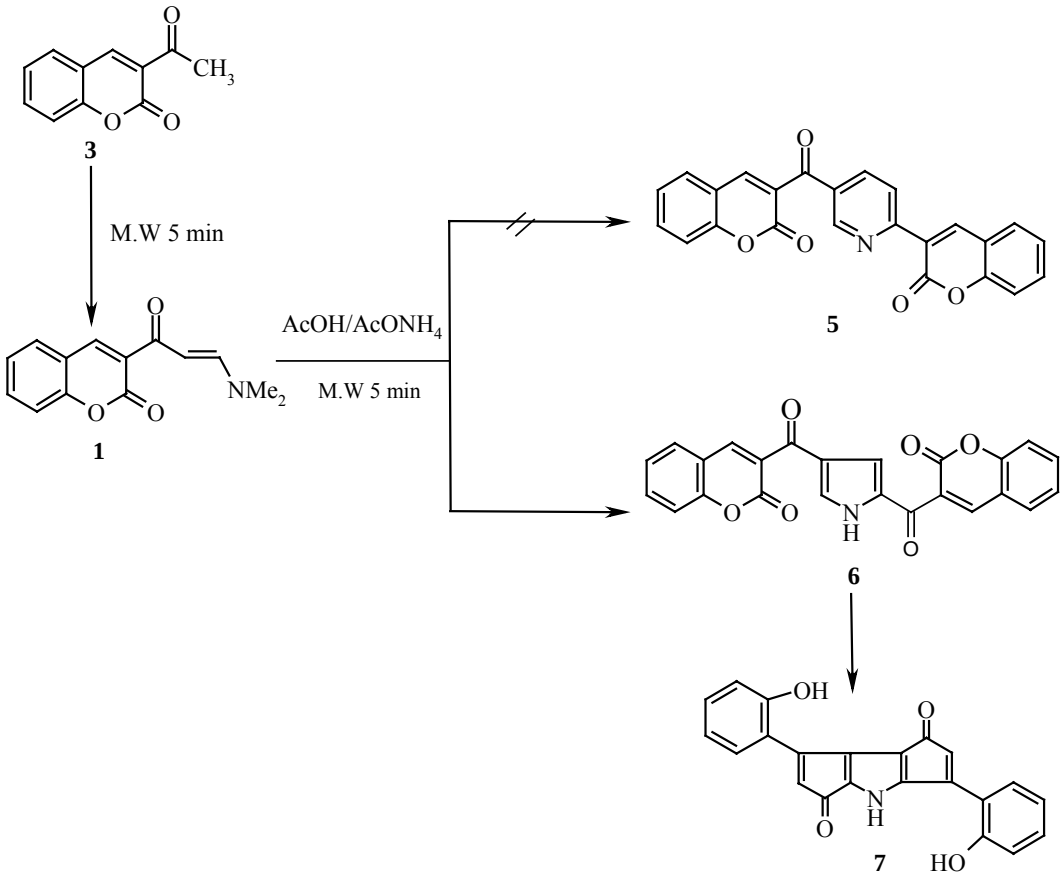
Introduction

The utility of microwaves in heterocyclic synthesis is now receiving considerable attention [1-4] and, although enaminones has been recently extensively utilized as precursors for the synthesis of heteroaromatics, the solventless reaction of enaminones with nucleophilic reagents under microwave irradiation has not, to our knowledge, been previously investigated. As a part of a recent project, aiming to explore potential utility of microwaves as an energy source for heterocyclic synthesis, I report here on synthesis of 3-heteroarylsubstituted coumarins and benzocoumarins of potential interest as pharmaceuticals and/or photochromic dyes [5-7] and investigate the possibility of conducting these reactions under microwave irradiation in addition to the standard thermal conditions.

Enaminones **1** and **2** were smoothly obtained by reacting compounds **3** and **4** with dimethylformamide dimethylacetal (DMFDMA) in a domestic microwave for a very short time, the yield being much higher than that obtained by conventional heating with a solvent. Compound **1** has been recently synthesized by Elnagdi *et al*., [8] by refluxing 3-acetylcoumarin with DMFDMA in xylene solution. However, under such conditions the yield of the enaminone was much lower than that obtained by the solventless procedure. Although the enaminones obtained may exist also in *cis*-form only the *trans*-forms **1** and **2** were obtained, as revealed by ^{1}H-NMR, which showed olefinic protons at δ = 6.53 ppm and δ = 8.17 ppm with J = 14Hz.

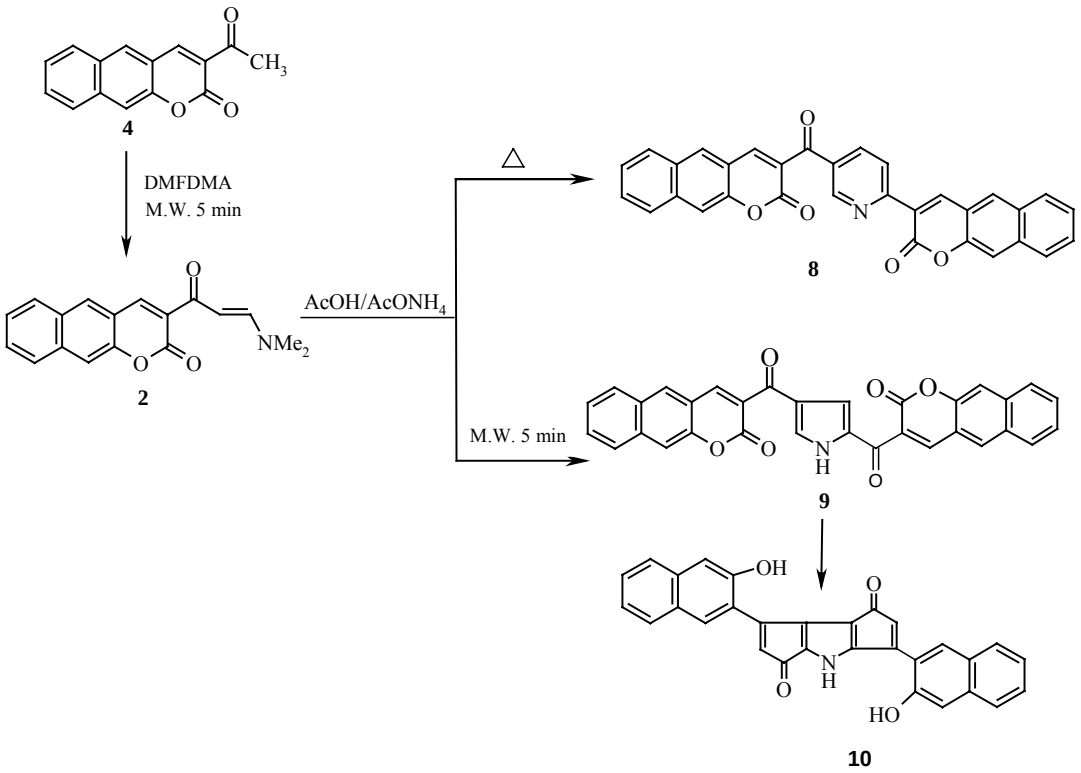
Although enaminone **1** has been reported earlier in literature [8] to yield pyridine derivative **5** on reflux in acetic acid in presence of ammonium acetate, treatment of **1** with acetic acid and ammonium acetate in a domestic microwave oven at full power has afforded a product of molecular formula $C_{22}H_{13}NO_4$, for which structure **7** is suggested. It is assumed that an initially formed 2,4-dicoumarinoyl pyrrole **6** undergoes a Nenitzescu like cyclization [9] and decarbonylation thus yielding **7** (Scheme 1).

Scheme 1



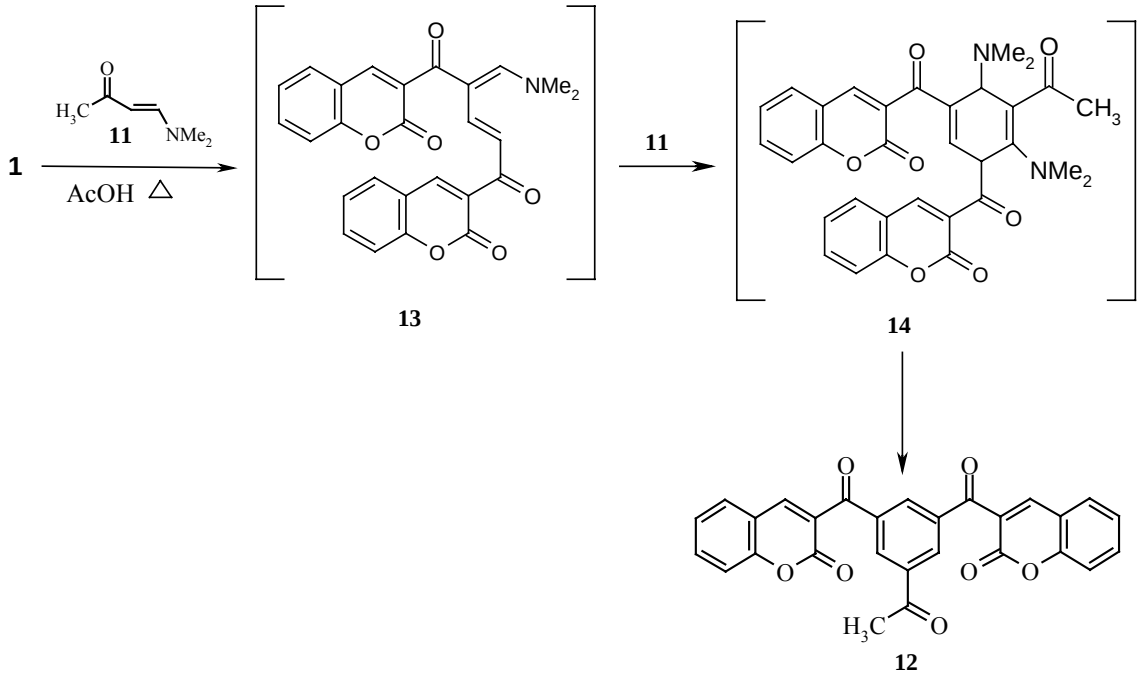
Similar to the behavior of **1**, compound **2** yielded pyridine derivative **8** on reflux in acetic acid in presence of ammonium acetate, while treatment of **2** with acetic acid and ammonium acetate in a domestic microwave oven at full power has afforded compound **10** (Scheme 2).

Scheme 2



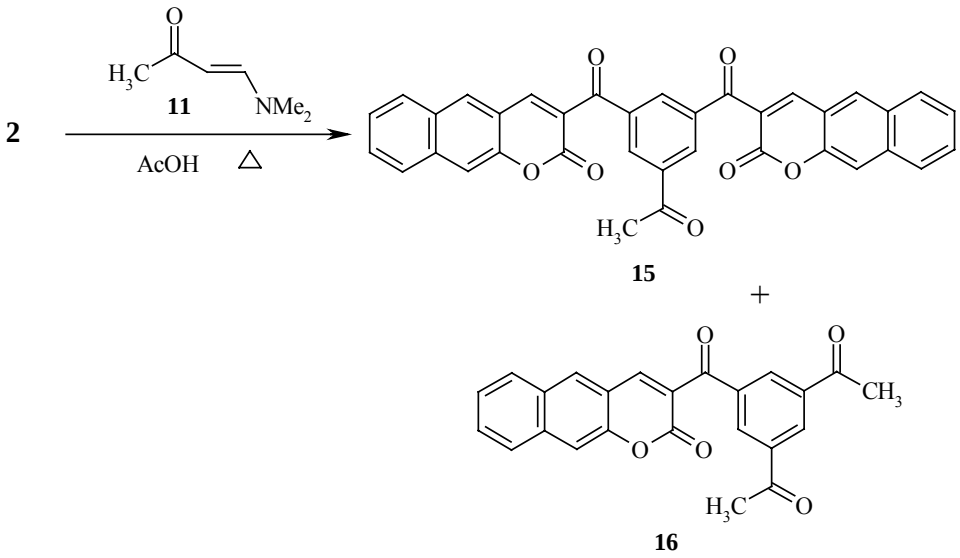
Thermal treatment of **1** with the enaminone **11** in acetic acid (Scheme 3) gave **12**, which may be a product of a thermal 2+2+2 cycloaddition or a product of initial dimerization of **1** into **13** that reacts with the enaminone **11** to yield **14,** that then aromatises to give the final isolated product **12** [10].

Scheme 3



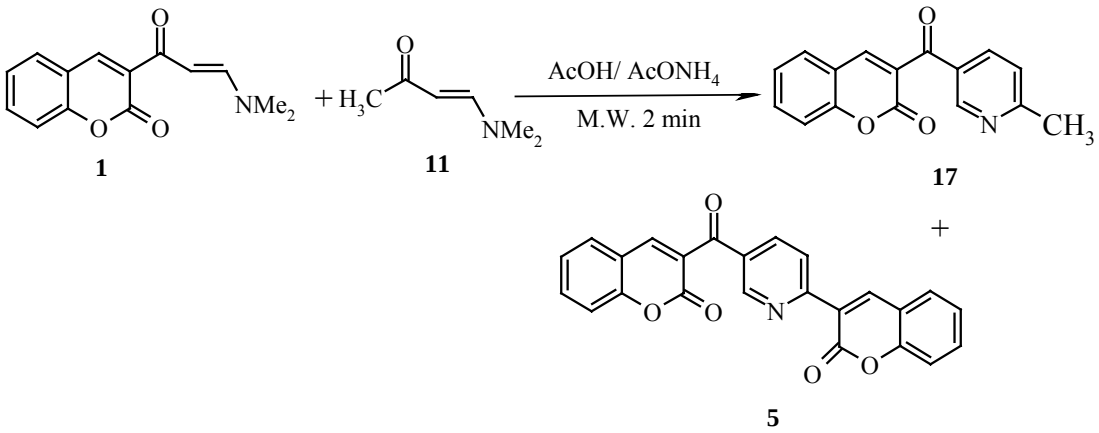
Under the same reaction conditions, compound **2** afforded a mixture of **15** and **16** (Scheme 4)

Scheme 4



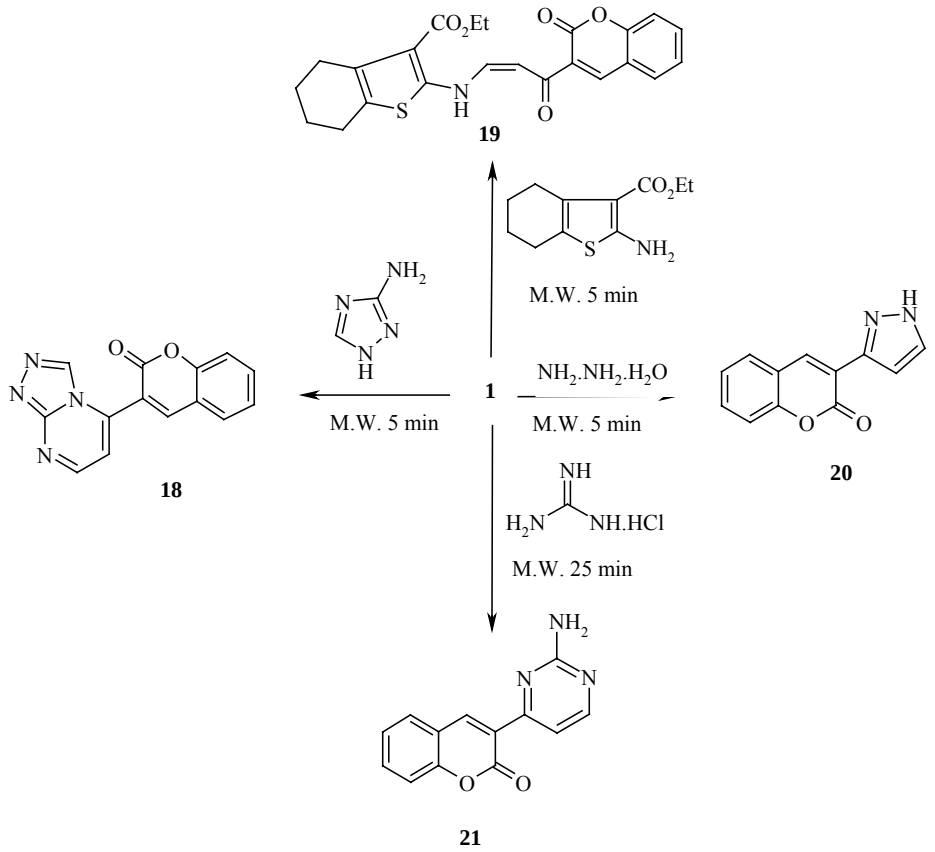
The reaction of **1** with **11** in a microwave oven had afforded a mixture of **17** and **5** (Scheme 5). Product **5** has been obtained earlier by Elnagid *et al.* via dimerization of **1** in presence of ammonium acetate [8].

Scheme 5

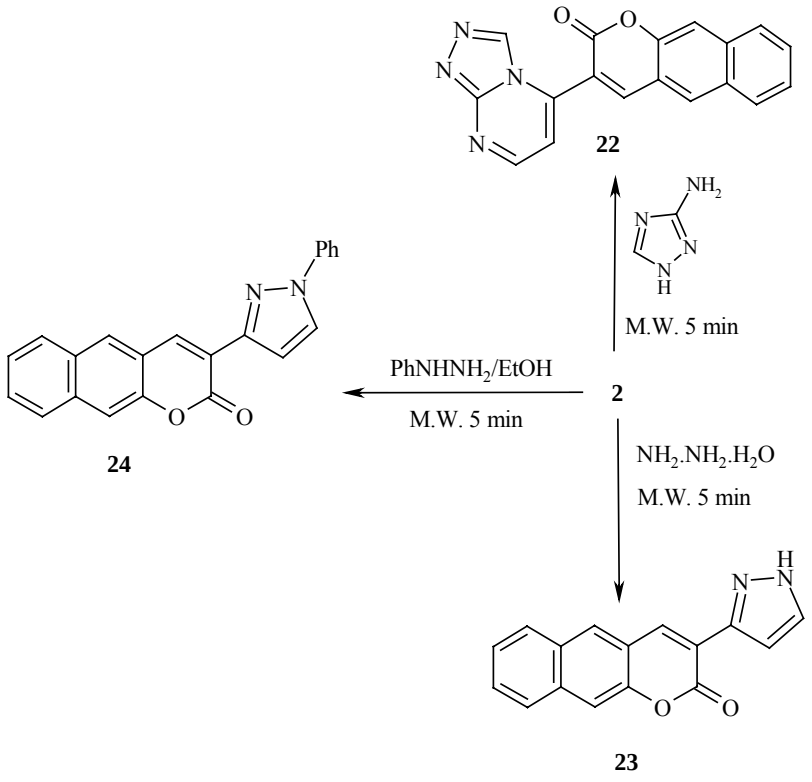


Compound **1** reacts readily with nitrogen nucleophiles in a microwave oven yielding products of addition, dimethylamine elimination and, in some cases, further cyclization affording a variety of 3-substituted heteroaromatic coumarin derivatives. For example, with 3(5)1,2,4-aminotriazole, the coumarinyl triazolopyrimidine derivative **18** has been obtained. The reaction of ethyl 2-aminotetrahydrobenzo[b]thiophene-3-caroboxylate with **1** afforded **19**, which was found to exist totally in *cis* form, as revealed by the ^{1}H-NMR spectrum which displayed olefinic protons at δ 5.69 and δ 6.61 ppm with J = 9Hz, typical for *cis* protons. It is likely that hydrogen bonding makes the *cis* form more stable than the *trans* one. Reaction of **1** with hydrazine hydrate afforded the pyrazolyl coumarin **20**. The reaction of **1** with guanidine hydrochloride in a microwave oven has afforded coumarinyl pyrimidine **21** in a very high yield (Scheme 6).

Scheme 6

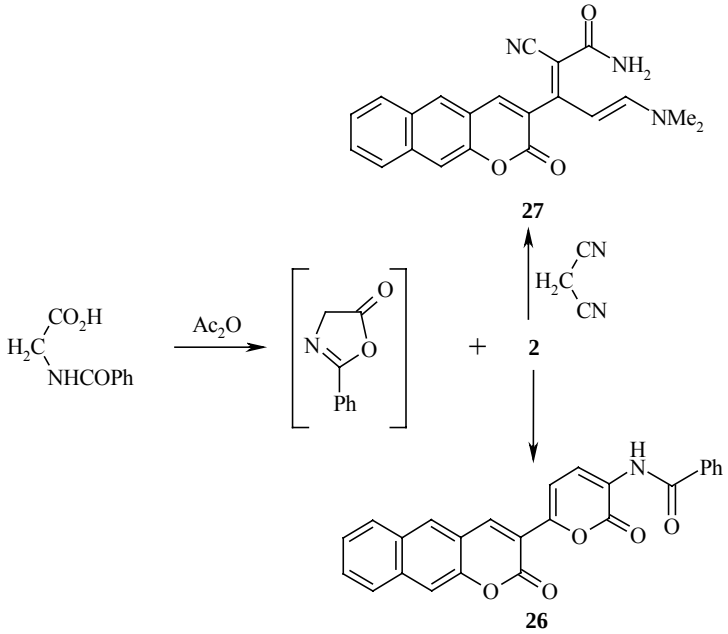


Scheme 7



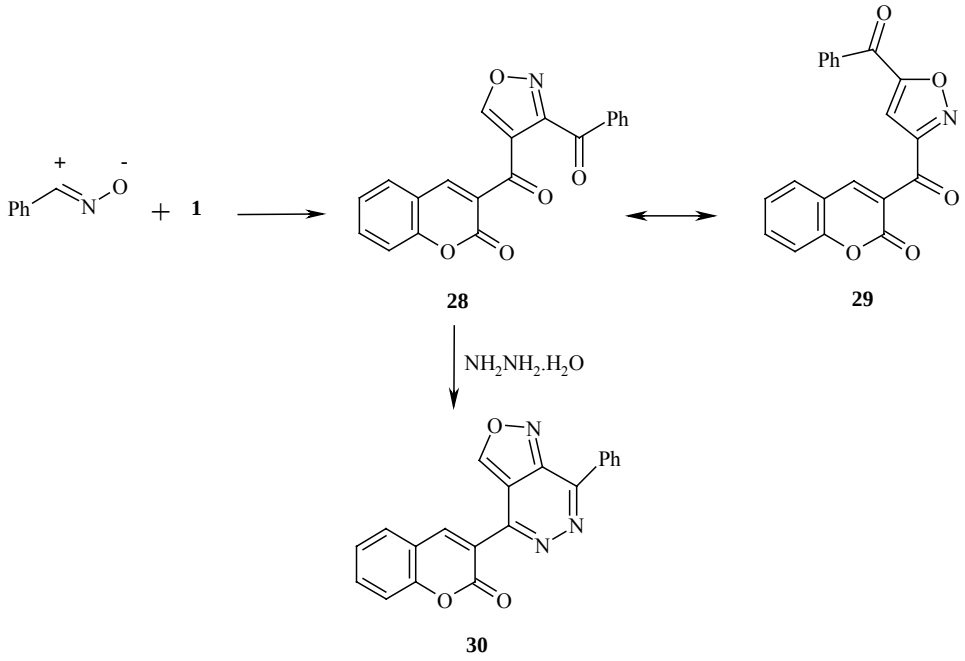
Similar to the behavior of **1**, compound **2** reacted with 3(5)1,2,4-aminotriazole to yield the benzocoumarinyl triazolopyrimidine derivative **22**, while with hydrazine hydrate and phenylhydrazine the pyrazolyl benzocoumarin derivatives **23** and **24** were formed, respectively (Scheme 7). Compound **2** also reacted with hippuric acid to yield the benzocoumarinyl α-pyrone **26**. It is believed that hippuric acid is first cyclized into isoxazolone **25** which then condense with **2** to yield **26**, while reaction of **2** with malononitrile afforded **27** (Scheme 8).

Scheme 8



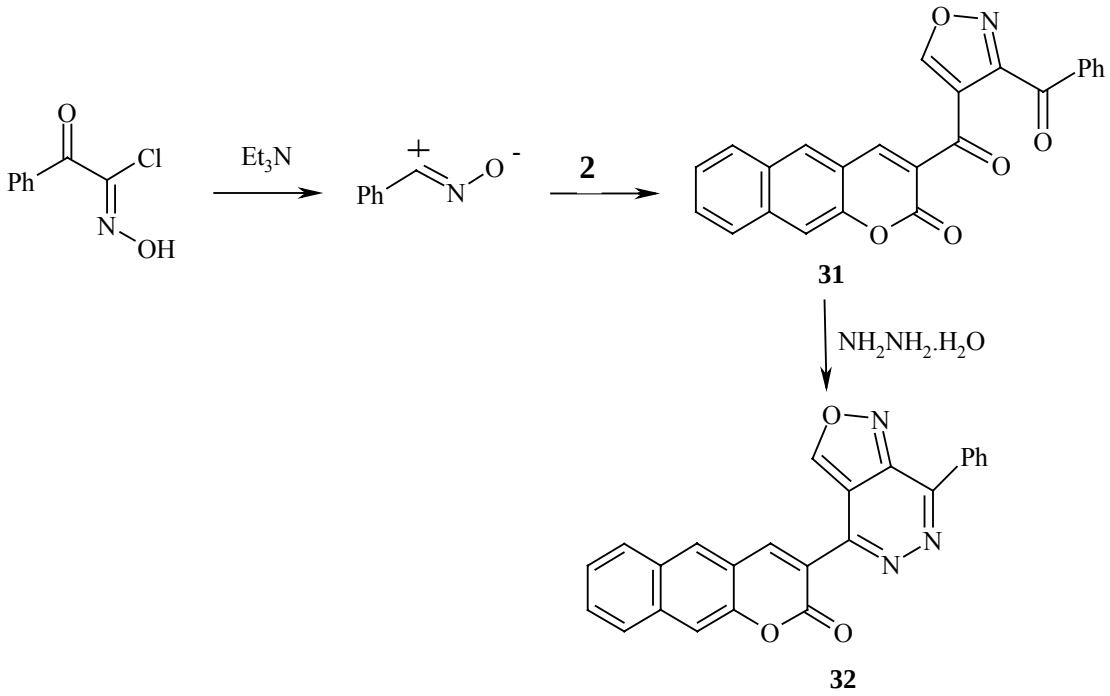
Structure **27** was assigned for this product based on ^{1}H-NMR data, that revealed two *trans* olefin doublets at δ= 5.83 and 6.88 ppm with J = 13Hz .

Scheme 9



Reaction of **1** with nitrile oxide afforded product that was considered to be the isoxazole derivative **28** rather than potential isomeric product **29**, based on the fact that this reaction product readily reacted with hydrazine hydrate to yield the coumarinyl isoxazolopyridazine **30** [11]. Also, reaction of compound **2** with nitrile oxide yielding the isoxazole derivatives **31** (Scheme 10), while reaction with nitrile imine afforded the pyrazole derivative **33** (Scheme 11).

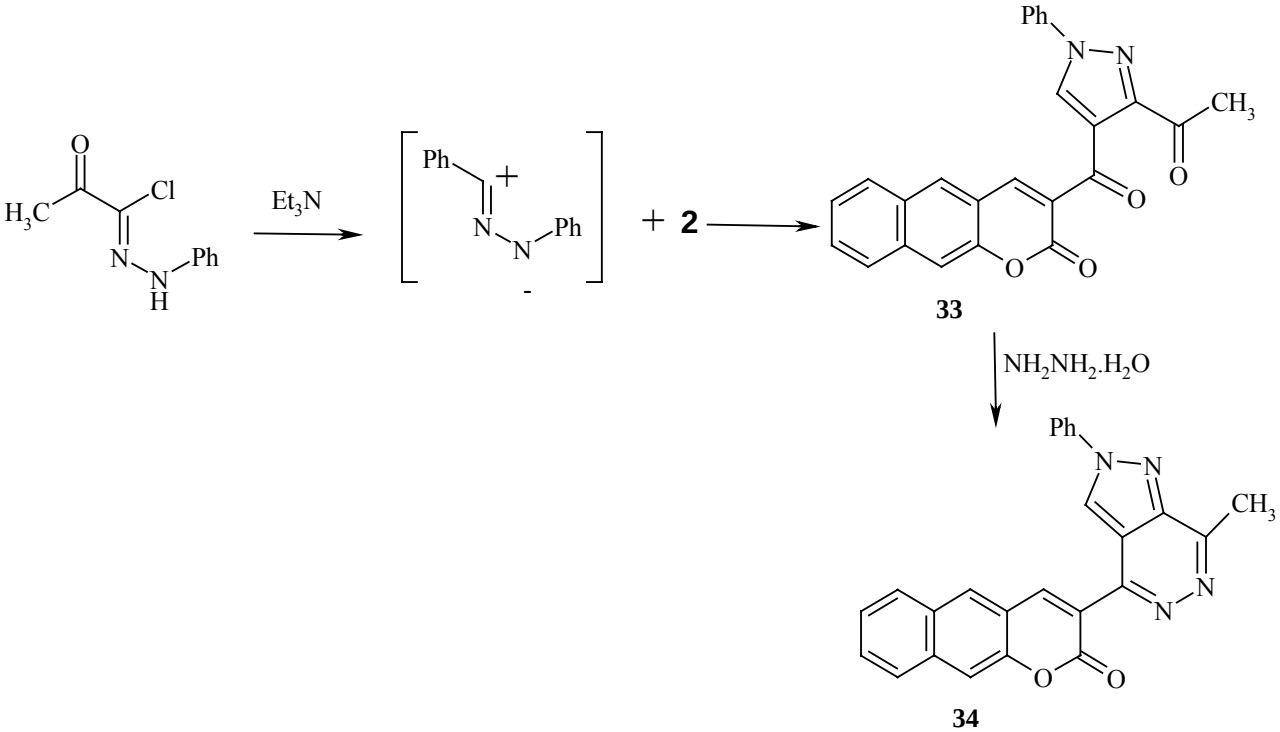
Scheme 10



31

32

Scheme 11



33

34

Experimental

General

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H-NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d_6) at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microwave irradiation was carried out using the commercial microwave oven (SGO 390 W). Elemental analyses were carried out at the Microanalytical Center of Cairo University, Egypt.

General Procedures for the Preparation of 1-(3-Coumarinyl)-3-dimethylamino-2-propen-1-one (**1**) *and 1-(3-Benzocoumarinyl)-3-dimethylamino-2-propen-1-one* (**2**) [8]:

Method A: Dimethylformamide dimethylacetal (DMFDMA, 0.1 mol) was added to 3-acetylbenzo-coumarin **3** (0.1 mol) in dioxane (50 mL), and the reaction mixture was refluxed for 6 hours. Removal of the solvent under reduced pressure yielded the crude product which was recrystallized from ethanol.

Method B: Compound **3** or **4** (0.1 mol) and DMFDMA (0.1mol) were placed in the microwave oven and irradiated at full power for 5 min., left to cool to room temperature and the solid formed was collected and recrystallized from ethanol.

Compound **2** was obtained as orange crystals (Method A: 85%; Method B: 95%), mp 157°C; IR: 1730 cm^{-1} (ring CO); ^{1}H-NMR: δ = 2.95 (s, 3H, NCH_3), 3.12 (s, 3H, CH_3), 6.11 (d, *J*=15 Hz, olefinic-H), 7.41-8.21 (m, 7H, arom-H), 8.60 ppm (d, *J*=15 Hz, olefinic-H); MS: M^+ (293); Anal. Calcd. for $C_{18}H_{15}NO_3$ (293.33): C, 73.71; H, 5.15; N, 4.78; Found: C, 73.52; H, 5.24; N, 4.85.

General Procedure for the Preparation of 3,7-Bis-(2-hydroxyphenyl)-4H-dicyclopenta[b,d]pyrrole-1,5-dione (**7**) *and 3,7-Bis-(3-hydroxynaphthalen-4-yl)-4H-dicyclopenta[b,d]pyrrole-1,5-dione* (**10**).

Compound **1** or **2** (0.01mol), ammonium acetate (0.01mol) and a few drops of glacial acetic acid were placed in the microwave oven and irradiated at full power for 3-10 min., left to cool to room temperature, and the solid product was then collected and crystallized from ethanol.

Compound **7** was obtained as dark yellow crystals (85%), mp 245°C; IR cm^{-1}: 3300 (OH), 3280 (NH); ^{1}H-NMR: δ = 6.81 (s, 2H, H-2 and H-6), 6.85-7.97 (m, 8H, arom-H), 8.97 (s, 1H, OH), 9.14 ppm (s, 1H, NH); MS: M^+ (355); Anal. Calcd. for $C_{22}H_{13}NO_4$ (355.35): C, 74.36; H, 3.69; N, 3.94; Found: C, 74.52; H, 3.64; N, 3.95.

Compound **10** was obtained as buff crystals (96%), mp 200°C; IR cm^{-1}: 3320 (NH), 3290 (OH); ^{1}H-NMR: δ = 6.82 (s, 2H, H-2 and H-6), 7.40-8.10 (m, 12H, arom-H), 8.97 (s, 1H, OH), 10.16 ppm (s,1H, NH); MS: M^+ (455); Anal. Calcd. for $C_{30}H_{17}NO_4$ (455.47): C, 79.11; H, 3.76; N, 3.08; Found: C, 79.22; H, 3.75; N, 3.10.

Procedure for the Preparation of 2-(Benzocoumarin-3′-yl)-5-(3-benzocoumarinoyl)pyirdine (**8**).

Compound **2** (0.01mol) and ammonium acetate (0.01mol) were refluxed in glacial acetic acid (30 mL) for 2 hr, then left to cool to room temperature. The solvent was then removed under vacuum and the residue cooled to deposit a solid, which was recrystallized from ethanol to give **8** as buff crystals (64%), mp 220°C; IR cm^{-1}: 1725 (ring C=O), 1681 (C=O); ^{1}H-NMR: δ = 7.31-7.79 (m, 12H, arom-H), 6.97-8.03 (d, 1H, pyridineH-3), 8.52 (s, 1H, pyridine H-6), 9.26 (d, 1H, pyridine H-4), 9.35, 9.61 ppm (2s, 2H, benzocoumarinyl H-4); MS: M^+ (495); Anal. Calcd. for $C_{32}H_{17}NO_5$ (495.50): C, 77.57; H, 3.46; N, 2.8; Found: C, 77.50; H, 3.50; N, 2.86.

General Procedure for the Preparation of 1-Acetyl-3,5-di(3-coumarinoyl)benzene (**12**), *1-Acetyl-3,5-di(3-benzocoumarinoyl)benzene* (**15**) *and* (*1,3-Diacetyl-5-(3-benzocoumarinoyl)benzene* (**16**)*:*

A mixture of either compound **1** or **2** (0.01 mol) and enaminone **11** (0.01mol) was refluxed in acetic acid for 2h, then left to cool to r.t. The target compounds separated as crystals that were collected by filtration and recrystallized from ethanol.

Compound **12** was obtained as buff crystals (66%), mp 178°C; IR cm^{-1}: 1720 (ring CO), 1689 (acetyl CO), 1660 (aroyl CO); ^{1}H-NMR: δ = 2.78 (s, 3H, CH_3), 7.54-7.97 (m, 8H, arom-H), 8.65 (s, 2H, H-4), 8.70 (s, 2H, H-2 and H-6), 9.12 ppm (s, 2H, coumarinyl H-4); MS: M^+ (464); Anal. Calcd. for $C_{28}H_{16}O_7$ (464.44): C, 72.41; H, 3.47; Found: C, 72.22; H, 3.55.

Compound **15** was obtained as buff crystals (49%), mp >300°C; IR cm^{-1}: 1700 (ring CO), 1685 (acetyl CO), 1658 (aroyl CO); ^{1}H-NMR: δ = 3.33 (s, 3H, CH_3), 7.54-8.31 (m, 12H, arom-H), 8.61 (s, 2H, H-4), 8.74 (s, 2H, H-2 and H-6), 9.22 ppm (s, 2H, benzocoumarinyl H-4); MS: M^+ (564); Anal. Calcd. for $C_{36}H_{20}O_7$ (564.56): C, 76.59; H, 3.57; Found: C, 76.60; H, 3.56.

Compound **16** was obtained as buff crystals (45%), mp >300°C; IR cm^{-1}: 1710 (ring CO), 1680 (acetyl CO); 1650 (aroyl CO); ^{1}H-NMR: δ = 2.72, 3.33 (2s, 3H, CH_3), 8.67 (s, 2H, H-4 and H-6), 8.72 (s, 1H, H-2), 7.68-8.41 (m, 6H, arom-H), 9.32 ppm (s, 1H, benzocoumarinyl H-4); MS: M^+ (384); Anal. Calcd. for $C_{24}H_{16}O_5$ (384.39): C, 74.99; H, 4.20; Found: C, 74.96; H, 4.25.

Preparation of 5-(3-Coumarinoyl)-2-methylpyridine (**17**) *and Compound* **5** [8]**:**

A mixture of compound **1** (0.01 mol), enaminone **11**, ammonium acetate (0.01mol) and a few drops of glacial acetic acid were placed in the microwave oven and irradiated at full power for 2 min., then left to cool to room temperature. The solid was collected and crystallized from ethanol.

Compound **17** was obtained as brown crystals (45%), mp 200°C; IR cm^{-1}: 1710 (ring CO), 1670 (aroyl CO); ^{1}H-NMR: δ = 2.55 (s, 3H, CH_3), 7.68-8.41 (m, 6H, arom-H and H-3), 8.76 (d, 1H, H-4), 9.32 (s, 1H, H-6), 8.81 ppm (s, 1H, coumarinyl H-4); MS: M^+ (265). Anal. Calcd. for $C_{16}H_{11}NO_3$ (265.27): C, 72.45; H, 4.18; N, 5.28; Found: C, 72.55; H, 4.25; N, 5.30.

Reaction of Compounds **1** or **2** *with 3(5)1,2,4-Aminotrizole and Aminocyclohexenothiophene: Preparation of 5-(Coumarin-3′-yl)-1,2,4-triazolo[4,3-a]pyrimidine* (**18**)**,** *5-(Benzocoumarin-3′-yl)-[1,2,4]triazolo-[4,3-a] pyrimidine* (**22**) *and 2-[3-Oxo-3-(2-oxo-2H-chromen-3-yl)-propenylamino]-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylic acid ethyl ester* (**19**)**:**

*Method A***:** To a solution of **1** or **2** (0.01 mol) either 3-amino-1H-1,2,4-trizole or aminocyclohexenothiophene (0.01 mol) in acetic acid/ethanol (1:1, 30 mL) were added. The reaction mixture was heated under reflux for 2hr, then left to cool. The solid was collected and recrystallized from ethanol.

Method B: Compound **1** or **2** (0.01mol) and 3-amino-1H-1,2,4-trizole or aminocyclohexenothiophene (0.01 mol) and a few drops of glacial acetic acid were placed in the microwave oven and irradiated at full power for 5 min., then left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **18** was obtained as pale brown crystals (65%), mp 252°C; IR cm^{-1}: 1730 (ring CO), 1660 (C=N); ^{1}H-NMR: δ = 7.38-7.73 (m, 4H, arom-H), 7.8 (d, 1H, pyrimidine H-6), 8.50 (s, 1H, coumarinyl H-4), 8.9 (s, 1H, triazole H-3), 9.21ppm (d, 1H, pyrimidine H-5); MS: M^+ (264). Anal. Calcd. for $C_{14}H_8N_4O_2$ (264.24): C, 63.64; H, 3.05; N, 21.20; Found : C, 63.74; H, 3.10; N, 21.26.

Compound **22** was obtained as yellow crystals (74%), mp 273 °C, microwave (90%). IR cm^{-1}: 1730 (ring CO), 1660 (C=N); ^{1}H-NMR: δ = 7.54-8.03 (m, 6H, arom-H), 8.07 (d, 1H, pyrimidine H-6), 8.50 (s, 1H, benzocoumarinyl H-4), 8.83 (s, 1H, triazole H-3), 9.23 ppm (d, 1H, pyrimidine H-5); MS: M^+ (314); Anal. Calcd. for $C_{18}H_{10}N_4O_2$ (314.30): C, 68.79; H, 3.21; N, 17.83; Found: C, 68.74; H, 3.10; N, 17.76.

Compound **19** was obtained as light red crystals (45%) mp 202°C; microwave (69%) mp 202°C; IR cm^{-1}: 3200 (NH), 1730 (ester CO), 1680 (ketone CO) 1648 cm^{-1} (ring CO); ^{1}H-NMR: δ = 1.39 (t, 3H, CH_3), 1.67-2.52 (m, 8H, cyclohexane-H), 4.32 (q, 3H, CH_2), 5.69, 6.61 (d, *J*=9Hz, 2H, olefin), 7.25-

8.22 (m, 6H, arom-H), 8.78 (s, 1H, coumarin H-4), 13.29 (s,1H, NH); MS: M^+ (423); Anal. Calcd. for $C_{23}H_{21}NO_5S$ (423.49): C, 65.23; H, 5.00; N, 3.31; Found: C, 65.25; H, 4.80; N, 3.46.

Reaction of Compounds **1, 2** *with Hydrazines: 3-(Coumarin-3′-yl)-pyrazole* (**20**), *3-(Benzocumarin-3′-yl)-pyrazole* (**23**) *and 3-(Benzocumarin-3′-yl)-1-phenylpyrazole* (**24**):

Method A: To a solution of **2** (0.01 mol) in ethanol (30 mL), either hydrazine hydrate or phenylhydrazine (0.01 mol) were added. The reaction mixture was heated under reflux for 4hr., then left to cool. The solid was collected and recrystallized from ethanol.

Method B: Compound **1** or **2** (0.01mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) was placed in the microwave oven and irradiated at full power for 5-10 min., left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **20** was obtained as light brown crystals (60%), mp 235°C; IR cm^{-1}: 3200 (NH), 1732 (CO), 1640 (C=N); ^{1}H-NMR: δ = 6.60 (d, 1H, pyrazole H-4), 7.25-7.82 (m, 4H, arom-H), 8.58 (m, 1H, pyrazole H-5), 9.09 (s, 1H, coumarin H-4), 11.27 ppm (s, 1H, NH); MS: M^+ (212); Anal. Calcd. for $C_{12}H_8N_2O_2$ (212.21): C, 67.92; H, 3.80; N, 13.20; Found: C, 67.82; H, 3.60; N, 13.13.

Compound **25** was obtained as yellow crystals (65%), mp 256°C, microwave (69%), mp 254°C; IR cm^{-1}: 3200 (NH), 1730 (CO), 1630 (C=N); ^{1}H-NMR: δ = 7.06 (d, 1H, pyrazole H-4), 7.25-8.22 (m, 6H, arom-H), 8.58 (m, 1H, pyrazole H-5), 9.29 (s, 1H, benzocoumarin H-4), 13.27 ppm (s, 1H, NH); MS: M^+ (262); Anal. Calcd. for $C_{16}H_{10}N_2O_2$ (262.27): C, 73.27; H, 3.84; N, 10.68; Found: C, 73.25; H, 3.80; N, 10.66**.**

Compound **24** was obtained as dark yellow crystals (59%), mp 230°C, microwave (61%), mp 231°C; ^{1}H-NMR: δ = 7.21 (d, 1H, pyrazole H-4), 7.35-8.32 (m, 11H, arom-H), 8.59 (m, 1H, pyrazole H-5), 9.29 ppm (s, 1H, benzocoumarin H-4); MS: M^+ (338); Anal. Calcd. for $C_{22}H_{14}N_2O_2$ (338.37): C, 78.09; H, 4.17; N, 8.28; Found: C, 78.12; H, 4.18; N, 8.30**.**

Reaction of Compound **1** *with Guanidine Hydrochloride*: *General Procedure for the Preparation of 2-Amino- 4-(coumarin-3′-yl) pyrimidine* (**21**):

Method A: To a solution of **1** (0.01 mol) in dry pyridine (20 mL) and (0.01 mol) of guanidine hydrochloride were refluxed for 3 hr, the solvent was reduced under vacuum to half its volume and the solid was collected and recrystallized from ethanol.

Method B: Compound **1** (0.01mol) and guanidine hydrochloride (0.01 mol) was placed in the microwave oven and irradiated at full power for 25 min., then left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **21** was obtained as dark yellow crystals (45%), mp 194°C, microwave (60%), mp 194°C; IR cm^{-1}: 3200 (NH_2), 1703 (ring CO); ^{1}H-NMR: δ = 7.48-7.90 (m, 4 H, arom-H), 7.26-8.03 (m, 6 H, arom-H), 8.23 (s, 1H, coumarin H-4), 8.40 (s, 1 H, NH_2), 8.81 (d, 1H, pyrimidine H-6), 9.02 (d, 1H, pyrimidine H-5); MS: M^+ (239); Anal. Calcd. for $C_{13}H_9N_3O_2$(239.24): C, 65.27; H, 3.79; N, 17.56; Found : C, 65.25; H, 3.80; N, 17.46.

3-Benzamido-6-(benzocoumarin-3′-yl) pyran-2-one (**26**):

Method A: Compound **2** (0.1mol) and hippuric acid (0.1mol) were refluxed in acetic anhydride (20 mL) for 1h, then left to cool at room temperature and poured into ice-cold water. The solid product thus formed was collected by filtration and recrystallized from ethanol.

Method B: Compound **2** (0.01mol), hippuric acid (0.01mol) and a few drops of acetic anhydride were placed in the microwave oven and irradiated at full power for 5 min., then left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **26** was obtained as red crystals (60%), mp 254 °C, and microwave (90%) IR cm^{-1}: 3309 (NH), 1690 (ring C=O), 1685 (ring C=O), 1660 (amide C=O); ^{1}H-NMR: δ = 7.38-8.09 (m, 11 H, arom-H), 8.21(s, 1H, pyran H-5). 8.62 (s, 1H, pyran H-4), 8.83 (s, 1H, benzocoumarin H-4) and 9.93 ppm (s, 1H, NH); MS: M^+ (409); Anal. Calcd. for $C_{25}H_{15}NO_5$ (409.40): C, 73.35; H, 3.69; N, 3.42; Found: C, 73.44; H, 3.72; N, 3.51.

3-(Benzocoumarin-3'-yl)-2-cyano-5-dimethylamino-2,4-pentadienoic amide (**27**):

Method A: To compound **2** (0.1 mol) and malononitrile (0.12 mol) in ethanol (30 mL), a few drops of piperidine were added .The reaction mixture was refluxed for 2h, then left to cool at room temperature and treatment with ethanol. The solid product, so formed, was collected by filtration and recrystallized from ethanol.

Method B: Compound **2** (0.1 mol) and malononitrile (0.12 mol) and a few drops of piperidine were added was placed in the microwave oven and irradiated at full power for 1 min., then left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **27** was obtained as dark red crystals (45%), mp 250 °C, and microwave (60%); IR cm^{-1}: 3370, (NH_2), 1670 (ring C=O), 1660 (C=O); ^{1}H-NMR: δ = 3.67, 3.69(2s, 6H, $N(CH_3)_2$),

5.83, 6.88 (d,1H,olefinic H), 7.18-8.03 (m, 6H, arom-H), 8.05 (s, 1H, benzocoumarin H-4) and 11.82 ppm (s, 1H, NH); MS: M^+ (359); Anal. Calcd. for $C_{21}H_{17}N_3O_3$(359.39): C,70.18; H,4.77; N,11.69; Found : C, 70.24; H, 4.72; N, 11.51**.**

General Procedures for the Preparation of 6-Benzoyl-3-(coumarin-3′-yl) isoxazole (**28**)*, 6-Benzoyl- 3-(benzocoumarin-3′-yl) isoxazole* (**31**) *and 3-Acetyl-4-(benzocoumarin-3′-yl) -1-phenylpyrazole* (**33**):

Method A: To a stirred solution of the appropriate hydroximoyl chloride (0.01mol), or hydrazonyl halide (0.01mol) and the appropriate enaminone **1** or **2** (0.01mol) in dry benzene (20 mL), triethylamine (0.2 mL) was added portionwise over a period of 30 min. The mixture was stirred at room temperature for 24-48 h and the precipitated triethylamine hydrochloride was filtered off, the filtrate was evaporated under reduced pressure and the residue was triturated with ethanol. The solid products were collected by filtration, washed with water and dried. Recrystallization from ethanol afforded the corresponding isoxazoles **28, 31** and the pyrazole **33**, respectively.

Method B: Compound **1** or **2** (0.01mol) and the appropriate hydroximoyl chlorides (0.01mol), or hydrazonyl halides (0.01mol) and a few drops of triethylamine were placed in the microwave oven and irradiated at full power for 25 min., then left to cool to room temperature and the solid was collected and recrystallized from ethanol.

Compound **28** was obtained as dark yellow crystals (41%), mp 165°C, microwave (54%); ^{1}H-NMR: δ = 7.61-8.31 (m, 9H, arom-H) 8.91 (s, 1H, coumarin H-4) and 9.36 ppm (s, 1H, H-5); MS: M^+ (345); Anal. Calcd. for $C_{20}H_{11}NO_5$ (345.31): C, 69.57; H, 3.21; N, 4.06; Found: C, 69.89; H, 3.17; N, 4.12**.**

Compound **31** was obtained as yellowish green crystals (45%), mp 190°C, microwave (54%); ^{1}H-NMR: δ = 7.61-8.71 (m, 11H, arom-H), 9.42 (s, 1H, benzocoumarin H-4) and 10.03 (s, 1H, H-5); MS: M^+ (395); Anal. Calcd. for $C_{24}H_{13}NO_5$ (345.37): C, 72.91; H, 3.31; N, 3.54; Found: C, 72.89; H, 3.32; N, 3.62.

Compound **33** was obtained as dark yellow crystals (43%), mp 228 °C, microwave (55%); ^{1}H-NMR: δ= 2.92 (s, 3H, CH_3), 7.58-8.59 (m, 11H, arom-H) 9.17 (s, 1H, benzocoumarin H-4) and 9.27 ppm (s, 1H, H-5); MS: M^+ (408); Anal. Calcd. for $C_{25}H_{16}N_2O_4$ (408.42): C, 73.52; H, 3.95; N,6.86; Found: C, 73.54; H, 4.00; N, 6.91.

Reaction of the Isoxazoles **28, 31** *and the Pyrazole* **33** *with Hydrazine Hydrate: General Procedure for the Preparation of 4-(Coumarin-3′-yl)-7-phenylisoxazolo[3,4-d]pyridazine* (**30**)*, 4-(Benzocoumarin-3′-yl)-7-phenylisoxazolo[3,4-d]pyridazine* (**32**) *and 4-(Benzocoumarin-3′-yl)-7-methyl-2-phenyl-pyrazolo[3,4-d] pyridazine* (**34**):

A mixture of the appropiate isoxazole **28, 31** or the appropiate pyrazole **33** (0.01mol) and hydrazine hydrate (80%, 0.01 mL) in absolute ethanol (20 mL) was heated under reflux for 3-4h. The solvent was evaporated under reduced pressure and the residue was left to cool to room temperature. The solid products were filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide afforded the the isoxazolo[3,4-*d*]-pyridazines **30, 32** and pyrazolo[3,4-*d*]pyridazine **34,** respectively.

Compound **30** was obtained as dark yellow crystals (71%), mp 245 °C; ^{1}H-NMR: δ = 7.65-8.31 (m, 9H, arom-H), 9.11 (s, 1H, coumarin H-4) and 9.31ppm (s, 1H, H-5); MS: M^+ (341); Anal. Calcd. for $C_{20}H_{11}N_3O_3$ (341.33): C, 70.38; H, 3.25; N, 12.31; Found: C, 70.40; H, 3.18; N, 12.12 .

Compound **32** was obtained as yellow crystals (74%), mp 189 °C; ^{1}H-NMR: δ= 7.65-8.61 (m, 11H, arom-H), 9.14 (s, 1H, benzocoumarin H-4) and 9.41ppm (s, 1H, H-3); MS: M^+ (391); Anal. Calcd. for $C_{24}H_{13}N_3O_3$ (391.39): C, 73.65; H, 3.35; N, 10.74; Found: C, 73.70; H, 3.40; N, 10.78.

Compound **34** was obtained as orange crystals (73%), mp 230°C; ^{1}H-NMR: δ = 2.52 (s, 3H, CH_3), 7.45-8.49 (m, 11H, arom-H), 9.47(s, 1H, benzocoumarin H-4) and 9.07 ppm (s, 1H, H-3); MS: M^+ (408); Anal. Calcd. for $C_{25}H_{16}N_4O_2$ (404.13): C, 74.25; H, 3.99; N,13.85; Found: C, 74.34; H, 4.01; N, 13.90**.**

Table 1: Comparison between microwave and solution reactions

Product	Time/min		Yield %		m.p °C	
	Solvent *	MW #	Solvent *	MW #	Solvent *	MW #
1	360	5	75	96	165	165
2	360	5	73	95	157	157
5	30	2	65	55	265	267
7	-	5	-	85	-	245
8	120	-	64	-	220	-
10	-	3	-	96	-	200
12	120	-	66	-	178	-
15	120	-	49	-	>300	-
16	120	-	45	-	>300	-
17	-	2	-	45	-	200
18	360	5	70	65	250 [8]	252
19	120	5	45	69	202	202
20	240	5	60	60	237 [8]	235
21	180	25	45	60	194	194
22	120	5	74	90	273	273

23	240	5	65	69	256	254
24	240	5	59	61	230	231
26	60	5	60	90	254	254
27	120	1	45	60	250	250
29	1440	10	41	54	165	165
30	180	-	71	-	245	-
32	1440	10	45	54	190	190
33	180	-	74	-	189	-
34	1440	10	43	55	228	228
35	180	-	73	-	230	-

* Reflux in a solvent; #with microwave irradiation.

References

1. Caddick, S. *Tetrahedron*, **1995**, *51*, 10403.
2. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacqnault, P.; Mathe, D. *Synthesis,* **1998,** 1213.
3. Perreux, L.; Loupy, A. *Tetrahedron,* **2001**, *57*, 9199.
4. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron,* **2001**, *57*, 9225.
5. Al-Zaydi,K. M. J. *Saudi Chem. Society***, 2002**, 477.
6. Al-Zaydi, K. M.; Hafez, E. A.; Elnagdi, M. H. J. *Chem. Res***. 2000**, *(S)* 4, (M) 510.
7. Al-Naggar, A. A.; Abdel-Khalik, M. M.; Elnagdi M. H.J. *Chem. Res.* **1999,** *(S),* 648, *(M),* 2801
8. El-Taweel, F. M. A.; Elnagdi, M. H. J. *Het.chem.,* **200**, *38*, 981.
9. Mukhanova, T. I.; Panisheva, E. K.; Lyubchanskaya, V. M.; Alekssseeva, L. M.; Sheinker, Y.N; Granik,V. G. *Tetrahedron*, **1997**, *53*, 177.
10. Abdel-Khalik, M. M.; Elnagdi, M. H., *Synth. Commun.,* **2002**, *32* (2) 159.
11. Al-Zaydi, K. M.; Hafez E. A. A. J. *Chem. Res.* **1999** (S), 360, *(M),* 1621.

Sample Availability: Available from the author

© 2003 by MDPI (http://www.mdpi.org). Reproduction is permitted for noncommercial purposes.