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

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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 $^1\text{H}-\text{NMR}$, which showed olefinic protons at $\delta = 6.53$ ppm and $\delta = 8.17$ ppm with $J = 14\text{Hz}$.

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 $\text{C}_{22}\text{H}_{13}\text{NNO}_4$, 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](image)

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).
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].

Under the same reaction conditions, compound 2 afforded a mixture of 15 and 16 (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].

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-carboxylate 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 $\delta$ 5.69 and $\delta$ 6.61 ppm with $J = 9$Hz, 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).
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).

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

\textbf{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).
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 \(\delta\) 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 dimethylecetal (DMFDMA, 0.1 mol) was added to 3-acetylbenzocoumarin 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 (0.1 mol) 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: \(\delta = 2.95\) (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 (0.01 mol), ammonium acetate (0.01 mol) 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 formed 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: \(\delta = 6.81\) (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: \(\delta = 6.82\) (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)pyridine (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: \(\delta = 7.31\) - 7.79 (m, 12H, arom-H), 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 (arylon CO); \(^1\)H-NMR: \(\delta = 2.78\) (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 (arylon CO); \(^1\)H-NMR: \(\delta = 3.33\) (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 (arylon CO); \(^1\)H-NMR: \(\delta = 2.72\), 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 (0.01 mol) 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); ¹H-NMR: δ = 2.55 (s, 3H, CH₃), 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 C₁₆H₁₁NO₃ (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 Aminocyclohexeno thiophene: 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-triazole or aminocyclohexeno thiophene (0.01 mol) in acetic acid/ethanol (1:1, 30 mL) were added. The reaction mixture was heated under reflux for 2 hr, then left to cool. The solid was collected and recrystallized from ethanol.

Method B: Compound 1 or 2 (0.01 mol) and 3-amino-1H-1,2,4-triazole or aminocyclohexeno thiophene (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); ¹H-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), 9.21 ppm (d, 1H, pyrimidine H-5); MS: M⁺ (264). Anal. Calcd. for C₁₄H₈N₄O₂ (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); ¹H-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 C₁₈H₁₀N₄O₂ (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); ¹H-NMR: δ = 1.39 (t, 3H, CH₃), 1.67-2.52 (m, 8H, cyclohexane-H), 4.32 (q, 3H, CH₂), 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 C₂₃H₂₁NO₅S (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 (0.01 mol) 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); ¹H-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 C₁₂H₈N₂O₂ (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); ¹H-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 C₁₆H₁₀N₂O₂ (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; ¹H-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 C₂₂H₁₄N₂O₂ (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 (0.01 mol) 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 (NH₂), 1703 (ring CO); ¹H-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, NH₂), 8.81 (d, 1H, pyrimidine H-6), 9.02 (d, 1H, pyrimidine H-5); MS: M⁺ (239); Anal. Calcd. for C₁₃H₉N₃O₂ (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 (0.1 mol) and hippuric acid (0.1 mol) 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 (0.01 mol), hippuric acid (0.01 mol) 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); ¹H-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 C₂₅H₁₅NO₅ (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 (0.01 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, (NH₂), 1670 (ring C=O), 1660 (C=O); ¹H-NMR: δ = 3.67, 3.69(2s, 6H, N(CH₃)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 C₂₁H₁₇N₃O₃ (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%); ¹H-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 C₂₀H₁₁NO₅ (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%); ¹H-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 C₂₄H₁₃NO₅ (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%); ¹H-NMR: δ = 2.92 (s, 3H, CH₃), 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 C₂₅H₁₆N₂O₄ (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-phenylpyrazolo[3,4-d] pyridazine (34):
A mixture of the appropriate isoxazole 28, 31 or the appropriate pyrazole 33 (0.01 mol) and hydrazine hydrate (80%, 0.01 mL) in absolute ethanol (20 mL) was heated under reflux for 3-4 h. 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: $\delta$ = 7.65-8.31 (m, 9H, arom-H), 9.11 (s, 1H, coumarin H-4) and 9.31 ppm (s, 1H, H-5); MS: M$^+$ (341); Anal. Calcd. for C$_{20}$H$_{11}$N$_3$O$_3$ (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: $\delta$ = 7.65-8.61 (m, 11H, arom-H), 9.14 (s, 1H, benzocoumarin H-4) and 9.41 ppm (s, 1H, H-3); MS: M$^+$ (391); Anal. Calcd. for C$_{24}$H$_{13}$N$_3$O$_3$ (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: $\delta$ = 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$_4$O$_2$ (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     |
Reflux in a solvent; with microwave irradiation.

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*Sample Availability:* Available from the author

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