Studies With Enaminones: Synthesis of New Coumarin-3-yl Azoles, Coumarin-3-yl Azines, Coumarin-3-yl Azoloazines, Coumarin-3-yl Pyrone and Coumarin-2-yl Benzo[*b*]Furans

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3-Acetylcoumarine was condensed with dimethylformamide dimethylacetal (DMFDMA) to yield the enaminone, which reacts readily with hydroxylamine and with hydrazines to yield coumarin-3-ylisoxazoles and coumarin-3-ylpyrazoles respectively. Reaction of the enaminone with benzamidine hydrochloride and 3-amino-1,2,4-1*H*-triazole affords the pyrimidine and triazolo[3,4-*b*]pyrimidine. The enaminone reacts with hippuric acid and with the dithiocarboxylic acid to yield pyranones. The reaction of the enaminone with 3-amino-1*H*-1,2,4-triazole gives the triazolo[3,4-*b*]pyrimidine. The enaminone underwent self dimerization on reflux in acetic acid ammonium acetate to yield the coumarinyl pyridines and reacted with ketone under the same conditions to yield the pyridine. The reaction of the enaminone with 1,4-benzoquinone and 1,4-naphthoquinone gives benzofuryl coumarine derivatives.

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Enaminones are versatile reagents and their utility in heterocyclic synthesis has recently received a considerable attention [1-4]. In conjunction with our interest in synthesis of 3-heteroarylcoumarine derivatives as potential laser dyes [5], pharmaceuticals [6] and agrochemicals [7]; we report here an efficient synthesis of a variety of target molecules utilizing the readily obtainable 3-acetylcoumarine **1** as starting material. Thus, 3-acetylcoumarine **1** reacted with dimethylformamide dimethylacetal (DMFDMA) in refluxing xylene to yield the enaminone **2**. The ^{1}H-NMR spectrum of **2** shows that the *trans* isomer is formed exclusively based on coupled olefinic protons at δ 5.95 and δ = 8.5 ppm with J = 15 Hz (AB system). The enaminone **2** reacted with hydroxylamine hydrochloride in the presence sodium acetate in EtOH to yield a product that may be formulated as the isoxazolyl-coumarine **3** or **4**. Structure **3** was established as the product because it is identical with product obtained from the reaction of oxime **5** with DMFDMA in refluxing xylene. It is thus assumed that compound **3** is formed *via* initial addition of the hydroxylamine nitrogen with the carbonyl group in system **2** and the resulting product then cyclizes into the final isoxazole derivatives **3** (Figure 1).

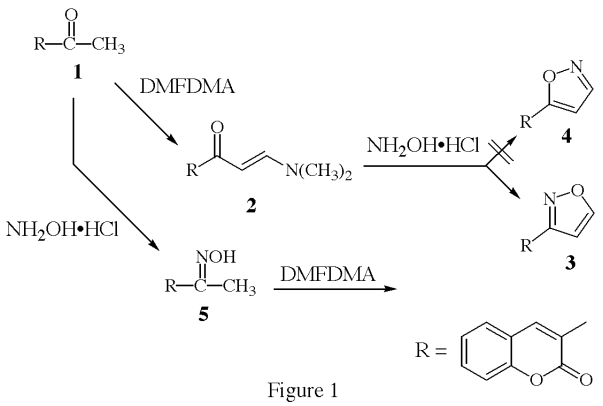

Figure 1

Similarly, compound **2** reacted with hydrazine hydrate and with phenylhydrazine to yield the pyrazole derivatives **6**. Attempts to obtain the pyrazole **7** from the reaction of the hydrazone **8** with DMFDMA failed. The enaminone **2** also reacted with benzamidine hydrochloride **9** to yield the 4-coumarinoyl pyrimidine **10** (Figure 2).

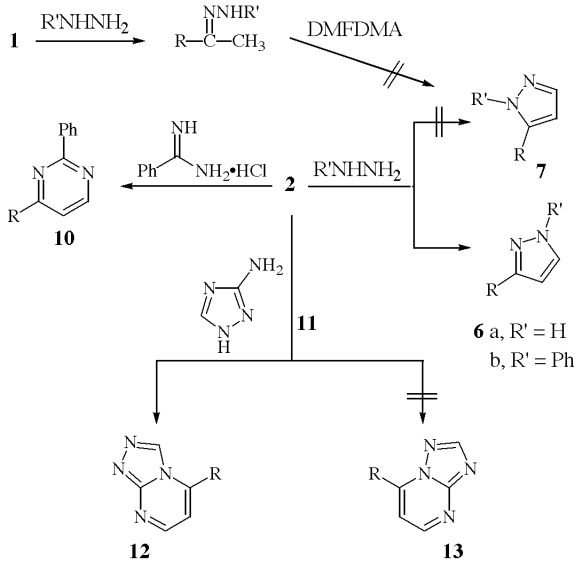

Figure 2

3-Amino-1*H*-1,2,4-triazole **11** reacted with **2** to yield a 1,2,4-triazolopyrimidine derivative that may be formulated as **12** or isomeric **13**. Structure **12** was established as the reaction product based on the ^{1}H-NMR spectrum, where the triazole proton is observed at δ 8.8 ppm, which is

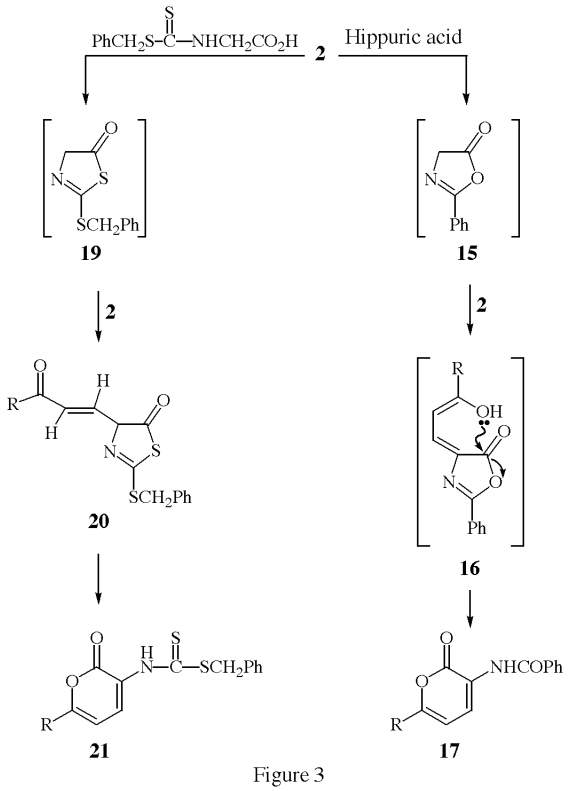

Figure 3

of **2** yielding **16** followed by further rearrange to give **17**. This is similar to the well known Kepe [8] pyranone synthesis that has recently been adopted by Elnagdi *et al*. [6] to enable synthesis of pyranones from reaction of the enaminone **2** with hippuric acid. Compound **2** also reacted with the dithiocarboxylic acid **18** to yield a product that may formulated as **20** and **21**. Formation of this product may be assumed to proceed *via* initial cyclization of the dithiocarboxylic acid derivatives into the thiazolone **19**. This then condensed with **2** *via* dimethylamine elimination to yield **20** that rearranges into a pyranone derivative **21** in a manner similar to that suggested to account for formation of pyranones from reaction of hippuric acid with **2** (Figure 3).

Refluxing of **2** in acetic acid/ammonium acetate afforded the pyridine derivative **23** (Figure 4). Compound **2** also reacted with **1** in acetic acid/ammonium acetate to yield the pyridine derivative **24**. Compound **2** reacted with 1,4-benzoquinone **25** and 1,4-naphthoquinonone **27** yielding the benzofuran **26** and naphthofuran **28**, espectively. It is believed that **2** first add the quinone to yield intermediate phenolic adduct that cyclizes *via* loss of dimethylamine to yield final isolable products. Similar reaction sequence has been recently proposed to account for formation of benzofuran from reaction of enaminones with quinones [4] (Figure 4).

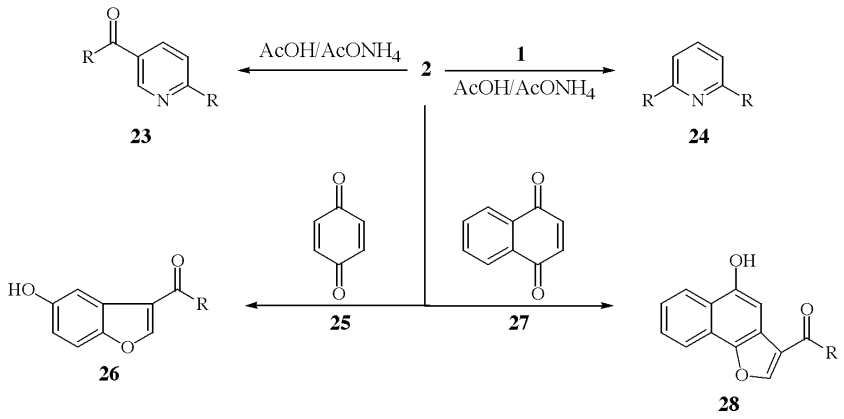

Figure 4

shifted from the expected value for the triazole proton of isomeric **13** by 1.0 ppm. This effect results from Van der Waals deshielding of the coumarinyl H-4 ,which in turn is deshielded and appears as singlet at δ 8.0 ppm.

Reacting **2** with hippuric acid **14** in acetic anhydride afforded the 3-pyranylcoumarine derivative **17**. These are assumed to be formed *via* initial cyclization of hippuric acid into the oxazolone **15** which then adds to the activated double bond system of another molecule

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded for KBr disks on a Shimadzu IR-740 spectrometer. ^{1}H NMR spectra were obtained on a Bruker AC-80 spectrometer with DMSO-d_6 as solvent and TMS as internal standards and chemical shifts expressed δ ppm. Mass spectra were measured on GC-MS INCOS XL Finnigan MAT. Elemental analyses were performed on LECO CHNS-932.

1-(3-Coumarinyl)-3-dimethylamino-2-propen-1-one (**2**).

Dimethylformamide dimethylacetal (1.19 g, 10 mmol) was added to 3-acetylcoumarin **1** (10 mmol) in xylene (50 ml), and the reaction mixture was refluxed for 6 hours. The removal of solvent under reduced pressure yielded the crude product which was crystallized from ethanol. Compound **2** was obtained as yellow crystals (75%), mp 165 °C; ir (potassium bromide): ν 1720 (ring CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 2.90 (s, 3H, NCH_3), 3.15 (s, 3H, CH_3), 5.95 (d, *J* = 15 Hz, olefinic-H), 7.35-7.90 (m, 5H, arom-H), 8.50 (d, *J* = 15 Hz, olefinic-H); ms : 243 (M^+).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 69.22; H, 5.34; N, 5.66.

3-(Coumarin-3'-yl)isoxazole (**3**).

A mixture of the enaminone **2** (2.43 g, 10 mmol) and hydroxylamine hydrochloride (10 mmol) in ethanol (50 ml), sodium acetate anhydrous (0.82g, 10 mmol) was refluxed for 6 hours, then left to cool. The formed precipitate was collected by filtration and crystallized from ethanol. Compound **3** was obtained as colorless crystals (65%), mp 195 °C; ir (potassium bromide): ν 1726 (ring CO) cm^{-1}; ^1H-NMR (dimethyl-d_6-sulfoxide): δ 7.25 (d, *J* = 3Hz, 1H, isoxazoleH-4), 8.75 (d, *J* = 3Hz, 1H, isoxazole H-5) 7.41-8.0 (m, 4H, Ar-H), 8.9 (s, 1H, coumarin H-4); ms: 213 (M^+).

Anal. Calcd. for $C_{12}H_7NO_3$: C, 67.61; H, 3.31; N, 6.57. Found: C, 67.50; H, 3.36; N, 6.42.

Reaction of Compound **2** with Hydrazines.

To a solution of **2** (2.43 g, 10 mmol) in ethanol (30 ml), either hydrazine hydrate (2 ml) or phenylhydrazine (1.5 ml) were added. The reaction mixture was heated under reflux for 4 hours, then left to cool. The solid products, so formed, were isolated by filtration, washed with ethanol and dried. Recrystallization from ethanol yielded colorless crystals of **6a,b**.

3-(Coumarin-3'-yl)pyrazole (**6a**).

Compound **6a** was obtained in 60% yield mp 237 °C; ir (potassium bromide): ν 3200 (NH), 1736 (ring CO), 1626 (C=N) cm^{-1}; ^1H-NMR (dimethyl-d_6 sulfoxide): δ 5.9 (d, *J* = 3 Hz, 1H, pyrazole H-4), 7.35-7.75 (m, 4H, Ar-H), 8.45 (d, *J* = 3 Hz, 1H, pyrazole H-5), 9.0 (s, 1H, coumarin H-4), 11.1 (s, 1H, NH); ms: 212 (M^+).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.78; H, 3.5; N, 13.11.

1-Phenyl-3-(coumarin-3'-yl)pyrazole (**6b**).

Compound **6b** was obtained in 60% yield, mp 135 °C; ir (potassium bromide): ν 1736 (ring CO), cm^{-1}; ^1H-NMR (dimethyl-d_6 sulfoxide): δ 6.8 (d, *J* = 3Hz, 1H, pyrazole H-4), 7.35-7.83 (m, 4H, Ar-H), 7.84 (d, *J* = 3Hz, 1H, pyrazole H-5), 8.21 (s, 1H, coumarin H-4); ms: 2289 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.89; H, 4.12; N, 9.69.

4-(Coumarin-3'-yl)-2-phenylpyrimidine (**10**).

A solution of **2** (2.43 g, 10 mmol) in dry pyridine (20 ml), and (1.55 g, 10 mmol) of benzamidine hydrochloride were refluxed for 3 hours. The solvent was reduced under *vacuo*, to half volume. The solid product, obtained, was isolated by filtration, dried and recrystallized from ethanol. Compound **10** was obtained as buff crystals, yield 70%, mp 185 °C; ir (potassium bromide): ν 1732 (ring CO), 1606 (C=N) cm^{-1}; ^1H-NMR (dimethyl-d_6 sulfoxide): δ 7.39-7.90 (m, 9H, Ar-H), 8.20 (s, 1H, coumarin H-4), 8.96 (d, *J* = 3Hz, 1H, pyridine H-6), 9.03 (d, *J* = 3Hz, 1H, pyrdine H-5); ms: 300 (M^+).

Anal. Calcd. for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03; N, 9.33. Found: C, 75.5; H, 4.60; N, 9.41.

4-(Coumarin-3'-yl)-1,2,4-triazolo[4,3-*a*]pyrimidine (**12**).

A solution of **2** (2.43 g, 10 mmol) and (0.84 g, 10 mmol) of 3-amino-1*H*-1,2,4-triazole in (30 ml) ethanol/acetic acid (1:1), was refluxed for 6 hours. The solvent was removed by distillation under reduced pressure and the resulting solution was left to cool. The solid precipitate was collected by filtration and recrystallized from ethanol. Compound **12** was obtained as canary yellow crystals, yield 70%, mp 250 °C; ir (potassium bromide): ν 1729 (ring CO), 1653 (C=N) cm^{-1};^1H NMR (dimethyl-d_6 sulfoxide): δ 7.35-7.50 (m, 2H, arom-H), 7.60-7.73 (m, 2H, arom-H), 7.8-7.9 (d, *J* = Hz, pyrimidine H-5), 8.5 (s, 1H, coumarinyl H-4), 8.8 (s, 1H, triazole H-3), 9.1 (s, 1H, pyrimidine H-6); ms: 264 (M^+).

Anal. Calcd. for $C_{14}H_8N_4O_2$: C, 63.64; H, 3.05; N, 21.20. Found: C, 63.41; H, 4.60; N, 21.35.

General Procedure for the Preparation of 3-Substituted-6-(coumarin-3'-yl)pyran-2-one **17** and **21**.

A solution of **2** (2.43 g, 10 mmol) and appropriate amount of **14** or **18** (10 mmol) in acetic anhydride (50 ml), was refluxed for 3 hours, then left to cool. The deposited solids were isolated by filtration and recrystallized to give **17** and **21**, respectively.

3-Benzamido-6-(coumarin-3'-yl)pyran-2-one (**17**).

Compound **17** was obtained as canary yellow crystals from DMF yield 75%, mp 284 °C; ir (potassium bromide): ν 3396 (NH), 1726 (ring CO), 1695 (ring CO), 1664 (amide CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 7.35-7.50 (m, 2H, arom-H), 7.3-7.6 (m, 7H, arom-H), 7.85 (d, *J* = 8 Hz, 1H, pyrane H-5), 8.30 (d, *J* = 8 Hz, 1h, pyrane H-4), 8.75 (s, 1H, coumarinyl H-4), 9.74 (s, 1H, NH); ms: 359 (M^+).

Anal. Calcd. for $C_{21}H_{13}NO_5$: C, 70.19; H, 3.65; N, 3.90. Found: C, 70.31; H, 4.10; N, 4.02.

3-Benzylthiocarboxamido-6-(coumarin-3'-yl)pyran-2-one (**21**).

Compound **21** was obtained as buff crystals from ethanol/DMF yield 70%, mp 225 °C; ir (potassium bromide): ν 3450 (NH), 1746 (CO), 1720 (ring CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 2.84 (s, 2H, CH_2), 6.78 (d, *J* = 8 Hz, 1H, pyrone H-4), 7.25-7.59 (m, 9H, Ar-H), 7.89 (d, *J* = 8 Hz, 1H, pyrone H-5), 8.30 (s, 1H, coumarinyl H-4), 8.34 (s, 1H, NH); ms: 421 (M^+).

Anal. Calcd. for $C_{22}H_{15}NO_4S_2$: C, 62.69; H, 3.59; N, 3.32. Found: C, 62.63; H, 3.41; N, 3.22.

2-(Coumarin-3'-yl)-5-(coumarin-3'-oyl)pyridine (**23**).

Compound **2** (2.43 g, 10 mmol) and (0.77g, 10 mmol) of ammonium acetate were refluxed in glacial acetic acid (30 ml) for 0.5 hour, then left to cool to room temperature. The precipitated material upon cooling was isolated by filtration and recrystallized from DMF to give **23** as buff crystals yield 65%, mp 265 °C; ir (potassium bromide): ν 1730 (ring CO), 1680 (CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 7.35-7.72 (m, 8H,

Ar-H), 7.89 (d, *J* = 8 Hz, 1H, pyridine H-3), 8.20 (d, *J* = 8 Hz, 1H, pyridine H-4), 8.50 (d, *J* = 8 Hz, 1H, pyridine H-5), 8.9, 9.0 (2s, 2H, coumarinyl H-4), 9.34 (s, 1H, NH); ms: 395(M^+).

Anal. Calcd. for $C_{24}H_{13}NO_5$: C, 72.91; H, 3.31; N, 3.54. Found: C, 72.85; H, 3.24; N, 3.46.

2,6-Bis(coumarin-3'-yl)pyridine (**24**).

A mixture of **2** (2.43 g, 10 mmol) and (1.88 g, 10 mmol) of 3-acetylcoumarin **1** in glacial acetic acid (30 ml) and (0.77 g, 10 mmol) of ammonium acetate, was refluxed for 1 hour. The precipitated material was isolated by filtration and recrystallized. Compound **24** was obtained as yellow crystals from ethanol/DMF yield 65%, mp 280 °C; ir (potassium bromide): ν 1730 (ring CO), 1673 (CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 7.6-8.4 (m, 11H, Ar-H), 9.03, 9.06 (2s, 2H, coumarinyl H-4); ms: 367 (M^+).

Anal. Calcd. for $C_{23}H_{13}NO_4$: C, 75.20; H, 3.57; N, 3.81. Found: C, 75.33; H, 3.61; N, 3.49.

General Method for Preparation of **26** and **28**.

To a stirred solution of **2** (2.43 g, 10 mmol) in glacial acetic acid (50 ml), each of *p*-benzoquinone and 1,4-naphthoquinone (10 mmol) was added. Stirring was continued over night at room temperature. The reaction mixture was evaporated *in vacuo* and the solid products obtained were isolated by filtration and recrystallized.

5-Hydroxy-3-(coumarin-3'-oyl)benzo[*b*]furan (**26**).

Compound **26** was obtained as colorless crystals from ethanol/DMF yield 70%, mp 284 °C; ir (potassium bromide): ν 3337 (OH), 1714 (ring CO), 1690 (CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 7.35-7.98 (m, 7H, Ar-H), 8.47 (s, 1H, OH); ms: 306 (M^+).

Anal. Calcd. for $C_{18}H_{10}O_5$: C, 70.59; H, 3.29. Found: C, 70.31; H, 3.46.

5-Hydroxy-3-(coumarin-3'-oyl)naphtho[1,2-*b*]furan (**28**).

Compound **28** was obtained as yellow crystals from DMF yield 60%, mp 280 °C; ir (potassium bromide): ν 1725 (ring CO), 1640 (CO) cm^{-1}; ^1H NMR (dimethyl-d_6 sulfoxide): δ 7.34-8.29 (m, 9H, Ar-H), 8.50 (s, 1H, OH), 9.0 (s, H, coumarinyl H-4), 10.4 (s, 1H, CHO).

Anal. Calcd. for $C_{22}H_{12}O_5$: C, 74.16; H, 3.39. Found: C, 74.23; H, 3.51.

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