A Simple Synthesis of Novel 2-Pyridones from Chalcones

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Several novel 2-pyridones were synthesized in good yields from a simple one-pot reaction by the condensation of different substituted chalcones and malonamide using sodium ethoxide in ethanol at room temperature. The structures of these 2-pyridones were elucidated from their ^1H, ^{13}C and infrared spectral data as well as their elemental analysis. Different 2-pyridones tautomers were obtained as the solvent of crystallization changes.

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A literature search revealed that a fair amount of work has been published on the condensation of α,β-unsaturated Michael acceptors with active methylene compounds [1-7]. For example, it has been reported that chalcones condensed with thioacetamide to give 2-pyridinethiones [8], with cyanoacetamide to give 2-pyridones [9], and with ethyl cyanoacetate to give 8-oxaquinoline derivatives [10]. In addition, several 2-pyridone derivatives were synthesized using different starting materials [11-14].

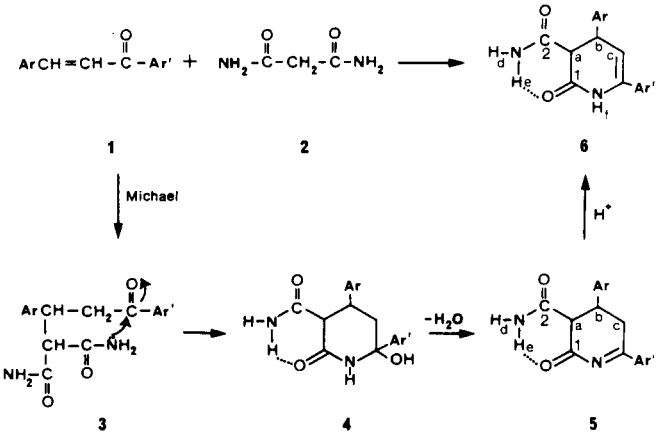
Because of our long standing interest in this laboratory [15-21] in the condensation reations of chalcones with active methylene compounds and because of the importance of the 2-pyridone derivatives as potentially physiologically active comopunds [22-23] we expand our synthetic activity along these lines to include the synthesis of novel highly substituted 2-pyridone derivatives *via* the basic condensation of different substituted chalcones with malonamide.

This simple and convenient reaction is easily performed in ethanol at room temperature by stirring a mixture of chalcones **1** and malonamide **2** in 1:1 molar ratio using sodium ethoxide as base for a period of 1-2 hours. White or light yellow precipitates were formed which upon filtration and recrystallization from ethanol or acetic acid/water afforded the 2-pyridone derivatives **5** or **6** respectively, as shown in Scheme 1. These 2-pyridones crystallized as white solids in good yields.

The structures of the 2-pyridone-3-carboxamide derivatives **5a-e** and **6a-e** were confirmed by their consistent infrared, proton and carbon-13 spectral data and by their elemental analysis as well. The infrared spectra of the 2-pyridones **5** and **6** display strong absorption bands at around 1685 and 1710 cm^{-1} characteristic of the carbonyl group stretching frequency in the amide and cyclic imide systems, respectively. Another bands at 3400, 3430 and 3370 cm^{-1} due to N-H stretching frequency were also observed in addition to the carbon carbon double bond absorption band at 1640 for the **6**-system compounds. However, only two N-H frequency bands were observed for the **5** system compounds.

On the other hand, the two 2-pyridone systems **5** and **6** showed completely different ^1H nmr spectra. For example, the 2-pyridones **5**, showed a doublet at around δ 3.50 due to H_a, a multiplet at around 2.95 due to H_b and a doublet of doublet at 3.60 due to H_c. In this system only two N-H proton signals were observed and exchanged with deuterium oxide. Atom H_e was more highly deshielded than H_d and this is expected as a result of the formation of six-membered hydrogen bonded ring.

Scheme 1



Chalcone	Ar	Ar'	Pyridone
1a	Phenyl	Phenyl	**5a**
1b	2-Tolyl	4-Chlorophenyl	**5b**
1c	3,4-Dichlorophenyl	4-Methoxyphenyl	**5c**
1d	2,4-Dimethoxyphenyl	4-Chlorophenyl	**5d**
1e	4-Tolyl	4-Chlorophenyl	**5e**
1f	4-Chlorophenyl	4-Bromophenyl	**6a**
1g	4-Methoxyphenyl	4-Chlorophenyl	**6b**
1h	4-Chlorophenyl	4-Chlorophenyl	**6c**
1i	4-Tolyl	Phenyl	**6d**
1j	4-Tolyl	4-Bromophenyl	**6e**

The ^1H nmr spectra of the 2-pyridones **6** showed a doublet at around 3.45 due to H_a, a double doublet at around 4.21 due to H_b and the vinylic proton H_c gave a doublet at 5.45. The 2-pyridones **6** showed two N-H signals which exchanged upon the addition of deuterium oxide. The third imide proton H_f gave a signal at 9.90. The fact that H_f proton in system-**6** compounds appeared as a

doublet (J = 3 Hz) in some nmr spectra indicated the presence of long range coupling between H_c and H_f where both protons lie in a rigid W geometry. Moreover, the decoupled ^{13}C nmr spectral data of pyridones **5** show the presence of both the α,β-unsaturated keto group and the amide carbonyl group. For example, **5a** shows two singlets at 196.2 due to the keto carbonyl carbon (C-1) and at 169.9 characteristic of the amide carbonyl carbon (C-2). On the other hand, pyridones **6** show the presence of both the imide and the amide carbonyl carbons. As a representative example **6a** shows two singlets at 169.4 and 168.0 due to the imide and amide carbonyl carbons (C-1) and (C-2), respectively.

The formation of the heterocyclic 2-pyridones may be explained by the mechanism depicted in Scheme 1. It involves a simple Michael addition to give the adduct **3** followed by nucleophilic addition of the nitrogen unshared electron pair at the ketone group with cyclization to afford the 6-hydroxy-2-pyridones **4**. Elimination of water molecule furnished the 2-pyridone system **5**, which upon treatment with acid gave the 2-pyridones **6**.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and were uncorrected. Proton and carbon-13 nuclear magnetic resonance spectra were measured on a Brucker WP-80 SY spectrometer. The infrared spectra were recorded as potassium bromide disks using a Pye-Unicam SP3-100 spectrophotometer. Malonamide was purchased from Aldrich Chemical Company, Elemental analyses were carried out at the M-H-W Laboratories, Phoenix, Arizona.

General Procedure for the Reaction of Chalcones **1a-j** with Malonamide **2**.

To a freshly prepared sodium ethoxide solution (0.017 mole of sodium metal was dissolved in 150 ml of absolute ethanol), 0.017 mole of malonamide was added with stirring. To this mixture, 0.017 mole of chalcone was added with continuous stirring for the appropriate time at room temperature after which a solid separated, collected by suction filtration, washed with cold ethanol and recrystallized from the suitable solvent to give either the 2-pyridones **5** or **6**.

4,6-Diphenyl-2-oxo-2,3,4,5-tetrahydro-3-pyridinecarboxamide **5a**.

After 45 minutes reaction time, **5a** was obtained in 69% yield, mp 201-203° (ethanol); ^1H nmr (DMSO-d_6): δ 2.95 (m, 1H, Hb), 3.50 (d, 1H, Ha), 3.65 (dd, 2H, Hc), 7.81 (s, broad, exchanges with deuterium oxide, He), 6.80-8.05 (m, 10H, aromatic); ^{13}C nmr: δ 169.9 (C2), 196.2 (C1); ir (potassium bromide): ν 3400 (NH), 3370 (NH), 1710 (C=O, imide), 1685 (C=O, amide), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.82; H, 5.47; N, 9.63.

4-(4-Chlorophenyl)-2-oxo-6-(2-tolyl)-2,3,4,5-tetrahydro-3-pyridinecarboxamide **5b**.

After 65 minutes reaction time, **5b** was obtained in 72% yield, mp 221-222° (toluene-ethyl acetate); ^1H nmr (DMSO-d_6): δ 2.35 (s, 1H, Hb), 3.55 (d, 1H, Ha), 3.60 (dd, 2H, Hc), 7.75 (s, broad, 1H, exchanges with deuterium oxide, Hd), 7.89 (s, broad, 1H, exchanges with deuterium oxide, He), 6.75-7.93 (m, 8H, aromatic); ^{13}C nmr: δ 169.1 (C2), 195.7 (C1); ir (potassium bromide): ν 3365 (NH), 3405 (NH), 1720 (C=O, imide), 1680 (C=O, amide), 1625 (C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_2O_2Cl$: C, 66.96; H, 5.03; N, 8.22; Cl, 10.40. Found: C, 66.89; H, 5.07; N, 8.30; Cl, 10.45.

4-(3,4-Dichlorophenyl)-6-(4-methylphenyl)-2-oxo-2,3,4,5-tetrahydro-3-pyridinecarboxamide **5c**.

After 60 minutes reaction time, **5c** was obtained in 75% yield, mp 196-198° (ethanol); ^1H nmr (DMSO-d_6): δ 2.90 (m, 1H, Hb), 3.59 (d, 1H, Ha), 3.62 (dd, 2H, Hc), 3.75 (s, 3H, $ArOCH_3$), 7.80 (s, broad, 1H, exchanges with deuterium oxide, Hd), 7.95 (s, broad, 1H, exchanges with deuterium oxide, He), 6.80-8.05 (m, 7H, aromatic); ^{13}C nmr: δ 169.3 (C2), 196.3 (C1); ir (potassium bromide): ν 3410 (NH), 3380 (NH), 1715 (C=O, imide), 1685 (C=O, amide), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}N_2O_3Cl$: C, 64.14; H, 4.53; N, 7.87; Cl, 9.96. Found: C, 64.22; H, 4.22; N, 7.92; Cl, 10.10.

6-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-2-oxo-2,3,4,5-tetrahydro-3-pyridinecarboxamide **5d**.

After 75 minutes reaction time, **5d** was obtained in 68% yield, mp 227-228° (ethanol); ^1H nmr (DMSO-d_6): δ 2.94 (m, 1H, Hb), 3.35 (s, 3H, $ArOCH_3$), 3.55 (d, 1H, Ha), 3.62 (dd, 2H, Hc), 7.75 (s, broad, 1H, exchanges with deuterium oxide, Hd), 7.85 (s, broad, 1H, exchanges with deuterium oxide, He), 6.85-8.00 (m, 7H, aromatic); ^{13}C nmr: δ 169.3 (C2), 196.1 (C1); ir (potassium bromide): ν 3420 (NH), 3400 (NH), 1710 (C=O, imide), 1685 (C=O, amide), 1625 (C=N) cm^{-1}.

Anal. Calcd. for $C_{20}H_{19}N_2O_4Cl$: C, 62.10; H, 4.95; N, 7.24; Cl, 9.16. Found: C, 61.97; H, 4.91; N, 7.15; Cl, 9.25.

6-(4-Chlorophenyl)-2-oxo-6-(4-tolyl)-2,3,4,5-tetrahydro-3-pyridinecarboxamide **5e**.

After 80 minutes reaction time, **5e** was obtained in 73% yield, mp 215-217° (ethanol); ^1H nmr (DMSO-d_6): δ 2.37 (s, 3H, $ArCH_3$), 2.97 (m, 1H, Hb), 3.60 (d, 1H, Ha), 3.62 (dd, 2H, Hc), 7.70 (s, broad, 1H, exchanges with deuterium oxide, Hd), 7.80 (s, broad, 1H, exchanges with deuterium oxide, He), 6.90-7.95 (m, 8H, aromatic); ^{13}C nmr: δ 168.9 (C2), 195.9 (C1); ir (potassium bromide): ν 3420 (NH), 3400 (NH), 1710 (C=O, imide), 1680 (C=O, amide), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_2O_2Cl$: C, 66.96; H, 5.03; N, 8.22; Cl, 10.40. Found: C, 67.19; H, 5.07; N, 8.26; Cl, 10.42.

6-(4-Bromophenyl)-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydro-3-pyridinecarboxamide **6a**.

After 90 minutes reaction time, **6a** was obtained in 80% yield, mp 225-226° (glacial acetic acid); ^1H nmr (DMSO-d_6): δ 3.45 (d, 1H, Hb), 4.21 (dd, 1H, Hb), 5.45 (d, 1H, Hc), 6.99 (d, 1H, exchanges with deuterium oxide, Hd), 7.15-7.91 (m, 9H, aromatic and He, integration becomes for 8H after exchanges with deuterium oxide), 9.89 (d, 1H, exchanges with deuterium oxide, Hf); ^{13}C nmr: δ 168.0 (C2), 169.4 (C1); ir (potassium bromide): ν 3420 (NH, amide), 3390 (NH, amide), 3370 (NH, imide), 1710 (C=O, imide), 1690 (C=O, amide), 1630 (C=C) cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O_2ClBr$: C, 53.29; H, 3.48; N, 7.89; Cl, 8.74. Found: C, 53.35; H, 3.52; N, 7.65; Cl, 8.92.

6-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydro-3-pyridinecarboxamide **6b**.

After two hours reaction time, **6b** was obtained in 79% yield, mp 218-220° (acetic acid-water); ^{1}H nmr (DMSO-d_6): δ 3.37 (d, 1H, Ha), 4.15 (dd, 1H, Hb), 5.45 (d, 1H, Hc), 6.82-7.63 (m, 10H, aromatic, Hd and He, the integration becomes for 8H after exchanges with deuterium oxide), 9.85 (s, broad, 1H, exchanges with deuterium oxide, Hf); ^{13}C nmr: δ 168.3 (C2), 169.1 (C1); ir (potassium bromide): ν 3410 (NH, amide), 3385 (NH, amide), 3360 (NH, imide), 1715 (C=O, imide), 1690 (C=O, amide), 1635 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_2O_3Cl$: C, 63.96; H, 4.80; N, 7.85; Cl, 9.94. Found: C, 64.15; H, 4.93; N, 7.97; Cl, 9.75.

4,6-Di-(4-Chlorophenyl)-2-oxo-1,2,3,4-tetrahydro-3-pyridinecarboxamide **6c**.

After 90 minutes reaction time, **6c** was obtained in 73% yield, mp 230-231° (acetic acid-water); ^{1}H nmr (DMSO-d_6): δ 3.37 (d, 1H, Ha), 4.22 (dd, 1H, Hb), 5.44 (dd, 1H, Hc), 7.01 (d, 1H, exchanges with deuterium oxide, Hd), 7.23-7.64 (m, 9H, aromatic and He, integration becomes for 8H after exchanges with deuterium oxide), 9.92 (d, 1H, exchanges with deuterium oxide, Hf); ^{13}C nmr: δ 168.9 (C2), 168.9 (C1); ir (potassium bromide): ν 3410 (NH, amide), 3390 (NH, amide), 3370 (NH, imide), 1710 (C=O, imide), 1685 (C=O, amide), 1630 (C=C) cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O_2Cl_2$: C, 59.85; H, 3.91; N, 7.76; Cl, 19.63. Found: C, 60.05; H, 4.03; N, 7.79; Cl, 19.76.

2-Oxo-6-phenyl-4-(4-tolyl)-1,2,3,4-tetrahydro-3-pyridinecarboxamide **6d**.

After 75 minutes reaction time, **6d** was obtained in 68% yield, mp 195-196° (acetic acid-water); ^{1}H nmr (DMSO-d_6): δ 3.41 (d, 1H, Ha), 4.29 (dd, 1H, Hb), 5.47 (dd, 1H, Hc), 6.93-7.89 (m, 11H, aromatic, Hd and He, integration becomes for 9H after exchanges with deuterium oxide), 9.95 (s, broad, 1H, exchanges with deuterium oxide, Hf); ^{13}C nmr: δ 168.5 (C2), 169.6 (C1); ir (potassium bromide): ν 3410 (NH, amide), 3385 (NH, amide), 3375 (NH, imide), 1715 (C=O, imide), 1685 (C=O, amide), 1635 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.75; H, 5.96; N, 9.13.

6-(4-Chlorophenyl)-2-oxo-4-(4-tolyl)-1,2,3,4-tetrahydro-3-pyridinecarboxamide **6e**.

After 90 minutes reaction time, **6e** was obtained in 71% yield, mp 265° dec (glacial acetic acid); ^{1}H nmr (DMSO-d_6): δ 3.46 (d, 1H, Ha), 4.14 (dd, 1H, Hb), 4.43 (dd, 1H, Hc), 7.04-7.65 (m, 8H, aromatic), 9.15-9.23 (s, broad, 2H, exchanges with deuterium oxide, Hd and He), 9.82 (s, broad, 1H, exchanges with deuterium oxide, Hf); ^{13}C nmr: δ 168.3 (C2), 169.6 (C1); ir (potassium bromide): ν 3410 (NH, amide), 3380 (NH, amide), 3370 (NH, imide), 1710 (C=O, imide), 1685 (C=O, amide), 1630 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}N_2O_2Br$: C, 59.24; H, 4.45; N, 7.27; Br, 20.74. Found: C, 59.33; H, 4.52; N, 7.31; Br, 20.89.

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