The Reaction of (Chlorocarbonyl)phenyl Ketene with Enaminones: A Novel Synthesis of Some 5-Acyl-4-hydroxy-2-(1*H*)-pyridinones and 7-Hydroxy-5-oxo-1,4-diazepin Derivative

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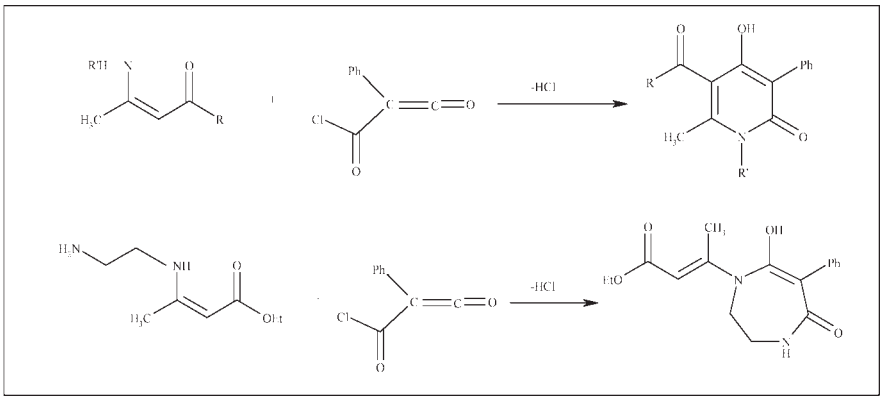

A series of substituted 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives has been prepared in a one-step procedure from condensation of (chlorocarbonyl)phenyl ketene with some enaminones which were prepared from 1,3-diketones, such as 2,4-pentanedione, 1-phenyl-1,3-butanedione, and ethyl acetoacetate in boiling toluene as a solvent. A mechanism is presented to account for the formation of the products. The overall sequence provides a simple and efficient route to prepare 3,4,5,6-tetrasubstituted 2-(1*H*)-pyridinone in good to excellent yields and in a short experimental time.

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INTRODUCTION

Heterocycles having a 2-pyridinone framework are an extensively studied class of compounds, owing partly to their diverse biological activities such as antibacterial [1] and antifungal [2] agents for free radical scavengers [3]. Ring fused 2-pyridinones have also attracted attention as lead compounds for the preparation of selective anticancer drugs [4,5], antiviral agents [6], angiotensin-converting enzyme (ACE) inhibitors [7], as well as inhibitors of A β-peptide aggregation [8], which is believed to play an important role in amyloid formation in Alzheimer's disease. In addition, dihydro and tetrahydro derivatives of 2-pyridinones have been applied as scaffolds for the construction of constrained amino acids [9,10]. With all these diverse properties in mind, medicinal chemists often incorporate these motifs in the design of novel biologically active molecules.

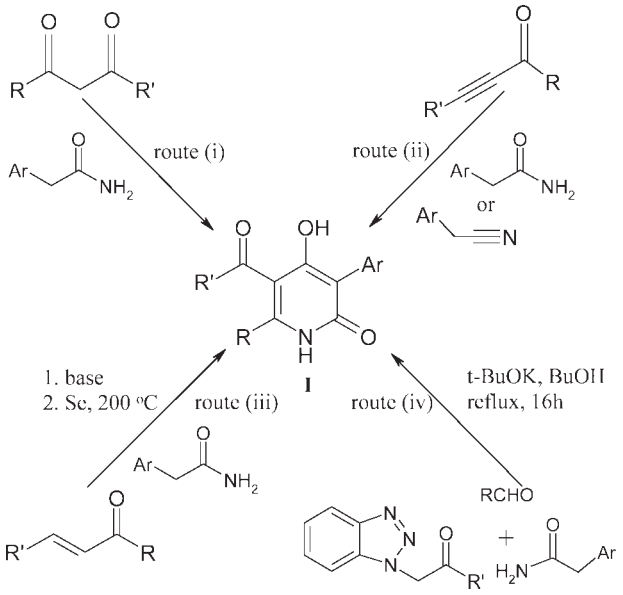
Ever since the first synthesis of 2-pyridinones was reported *via* a ferricyanide-mediated oxidation of pyridinium salts [11], many different methods for constructing these heterocycles in solution have appeared in the literature. Some of these reports include intramolecular Dieckmann like condensations [12], Michael additions [13,14], as well as cycloaddition [15] and cyclization procedures [16].

Fewer general methods exist for the preparation of 2-pyridinones substituted with aryl substituents and electron withdrawing groups such as CN, COR, COOR, and CONR2 at positions C3 and C5. Reported of 5-acyl-3-aryl-2-pyridinones usually include (Scheme 1) (i) reaction of 1,3-diketones with 2-arylacetamides (yields of **I** *ca*. 40%) [17]; (ii) Michael addition of arylacetamides or arylacetonitrile to 1,3-diaryl-2-propyne-1-ones affording products with limited diversity (3,4,6-triaryl substituted pyridinones in yields about 20%) [18]; (iii) Michael addition of 2-arylacetamides to 1,3-diaryl-2-propene-1-ones, is followed by cyclization subsequent oxidative aromatization of the intermediate dihydropyridinones with selenium at the high-temperature to yield 76–94% of the product I [19]; (iv) and finally synthesis *via* one-step [1 + 2 + 3] reactions of an aldehyde, α-benzotriazolyl ketone and arylacetamides [20].

RESULTS AND DISCUSSION

In continuing our interest in the synthesis of heterocyclic compounds by using chlorocarbonyl ketenes and

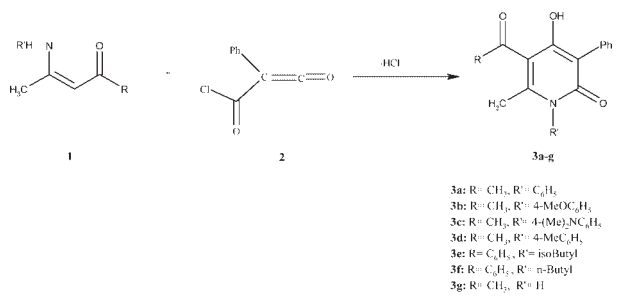
Scheme 1



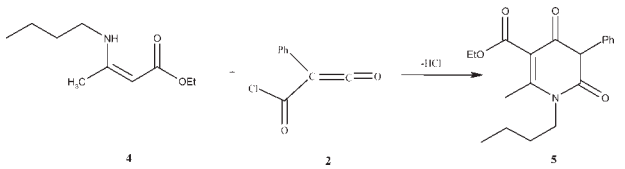
1,3-binucleophiles such as 1,3-diketones [21], amides [22,23] and thioamides [24]; in this article we wish to report a one-pot synthesis of 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives which were prepared in a one-step procedure from readily available (chlorocarbonyl)-phenyl ketene and enaminones as 1,3-binucleophile. This method provides an easy route to prepare 2(1*H*)-pyridinones in good to excellent yields and short experimental time (Scheme 2).

Enaminones are versatile synthetic intermediatates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones [25]. There are many reports in the literature on the functionalization of enaminone by the introduction of different substituents on the nitrogen, the α-carbon and the β-carbonylic carbon atoms. These derivatives have been extensively used for the preparation of a variety of heterocyclic systems including some natural products and analogues [26]. Thomas Kappe *et al*. [27], have reported

Scheme 2



Scheme 3



the synthesis of 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives from the reaction of enaminones with dialkyl malonates under harsh experimental conditions [low yields (42–68%) and also long reaction times].

The chemical importance and diversity of pyridinones have made these compounds important synthetic goals and have stimulated new methods and reagents for the preparation of these heterocyclic compounds. In an effort to extend the scope and generality of the condensation reaction (Scheme 1) (chlorocarbonyl)phenyl ketene **2** was treated with enaminones **1**. The only product formed under these conditions was 5-acyl-4-hydroxy-3-phenyl-2-(1*H*)-pyridinones **3** in excellent yields in a short experimental time.

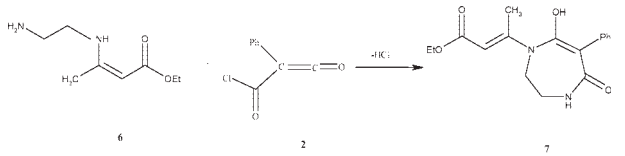
In this case, it was also found that the reaction of ethyl-3-(butylamino)-2-butenoate **4** with (chlorocarchloro-carbonyl)phenyl ketene **2** produce the corresponding pyridinone **5** (Scheme 3). It is pertinent to note that with the same experimental condition as the previous reaction different tautomer was formed.

The cycloaddition reaction of 4-[(2-aminoethyl) amino]-3-penten-2-one **6** with (chlorocarbonyl)phenyl ketene **2** resulted in the formation of ethyl (*E*)-3-(7-hydroxy-5-oxo-6-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-diazepin-1-yl)-2-butanoate **7** as the only product (Scheme 4).

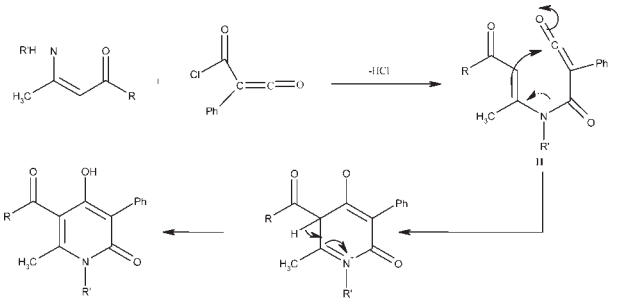
On the basis of this report, (chlorocarbonyl)aryl ketenes undergo a degenerate 1,3-shift of chlorine, as determined by ^{13}C NMR spectroscopy [28]. On the basis of our results, which was aforementioned, a plausible mechanism has been proposed for the reactions of (chlorocarbonyl)phenyl ketene with enaminones to yield 2-(1*H*)-pyridinone derivatives, as shown in Scheme 5. Initially, the NH group of enaminone as a good nucleophile will attack the acyl chloride of ketene, followed by ring closure of intermediate **2** to produce the product.

The structure of **3a-g** and compounds **5** and **7** were determined on the basis of their mass spectra, ^1H and

Scheme 4



Scheme 5



^{13}C NMR and IR spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectra of 4-hydroxy-3,6-disubstituted-2(1*H*)-pyridinone derivatives **3a-d** exhibited only one tautomer.

The ^{1}H NMR spectrum of **3a** showed four kinds of proton signals. One signal quite downfield (δ 10.70 ppm) which is the proton of enol OH and a multiplet (δ = 7.62–7.10) for the aromatic protons (10 H) along with two signals at (δ = 2.33 and 2.17 ppm) which were identified as an acyl group in position 5 and the other methyl group in position 6. The ^{13}C NMR and mass spectra are also in accordance with the proposed structure.

We have shown that the condensation reaction of (chlorocarbonyl)phenyl ketene with enaminones occurs efficiently in boiling toluene as a solvent, providing a convenient and rapid synthesis of 4-hydroxy-3,4,6-tri substituted-2(1*H*)-pyridinone in high yield, by a simple procedure and short experimental time. Furthermore, the products are solid and precipitate out from the reaction mixture and their purifications are simple.

EXPERIMENTAL

(Chlorocarbonyl)phenyl ketene was prepared according to the literature procedure [29]. The enaminones are known and were prepared according to the general procedure reported in the literature [30].

Toluene, hexane, diethyl ether, and THF were dried over sodium and distilled prior to use. Melting points were measured on a calibrated Gallenkamp melting point apparatus. IR spectra were measured with a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

General procedure (3a-d). To a stirred solution of corresponding enaminone (2 mmol) in 20 mL dry boiling toluene, a mixture of 0.36 g (chlorocarbonyl)phenyl ketene (2 mmol) in 5 mL dry THF was added dropwise over 2 min. The product was formed immediately as a color precipitate. The reaction mixture was cooled and the solid product was collected and recrystallized from dry ethyl acetate hexane.

5-Acetyl-4-hydroxy-6-methyl-1,3-diphenyl-2(1*H*)-pyridinone (3a). A 0.60 g red crystals, yield 95%, mp 224–226°C (dec.); IR (KBr): 3200–2500 (broad peak, OH), 1716, 1641 (C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.7 (1H, broad, OH), 7.62–7.10 (10H, m, arom), 2.33(3H, s, CH_3), 2.17(3H, s, CH_3); ^{13}C NMR (DMSO): δ 200.36, 163.90, and 163.13, 161.61, 131. 88, 131.15, 130.81, 129.65, 128.05, 128.00, 127.44, 123.28, 115.38, 103.79, 32.20, and 19.26; MS, *m/z* (relative intensity %): 319(M^{+}, 4), 291(5), 244(18), 216(32), 198(17), 160(17), 145(8), 127(15), 118(30), 93(38), 77(28), 65(20), 43(100). Anal. Calcd. For $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39%. Found: C, 74.89; H, 5.46; N, 4.16%.

5-Acetyl-4-hydroxy-1-(4-methoxy-phenyl)-6-methyl-3-phenyl-2(1*H*)-pyridinone (3b). A 0.61 g red crystals, yield 88%, mp 230–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1741, 1666(C=O), 1517 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.58(1H, broad, OH), 7.38–7.00 (9H, m, arom), 3.74 (3H, s, OCH_3), 2.49(3H, s, CH_3), 2.32(3H, s, CH_3); ^{13}CNMR (DMSO): δ 200.37, 163.89 and 163.15, 161.63, 158.75, 131.10, 130.65, 128.06, 128.51, 127.46, 124.11, 115.41, 114.79, 103.40, 55.45, 32.21, and 19.27; MS, *m/z* (relative intensity %): 349 (M^{+}, 2), 244 (25), 216(70), 198(18), 190 (16), 127(20), 123 (100), 118(35), 85(48), 80(35), 63(17), 43(90). Anal. Calcd. For $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01%. Found: C, 71.98; H, 5.50; N; 3.70%.

5-Acetyl-1-(4-dimethylaminophenyl)-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3c). A 0.62 g yellow crystals, yield 86%, mp 235–238°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1741, 1666 (C=O), 1535 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.37 (1H, broad, OH), 7.78–7.25 (9H, m, arom), 3.03 (6H, s, $2CH_3$), 2.05 (3H, s, CH_3), 1.93 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.93 (3H, s, CH_3); ^{13}CNMR (DMSO): δ 200.10, 168.74, and 162.25, 159.67, 146.83, 132.81, 130.84, 129.34, 127.78, 121.34, 110.17, 100.17, 42.67, 32.66, 19.38; MS, *m/z* (relative intensity %): 362 (M^{+}, 40), 347(5), 334(10), 294(15), 203(65), 187 (42), 178(28), 161(38), 135(95), 121(38), 105(25), 91(100), 77(48), 65(68), 50(27). Anal. Calcd. For $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73%. Found: C, 72.60; H, 6.20; N, 7.53%.

5-Acetyl-4-hydroxy-6-methyl-3-phenyl-1-*p*-toly1-2(1*H*)-pyridinone (3d). A 0.61 g red crystals, yield 92%, mp 228–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641 (C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.63 (1H, broad, OH), 7.49–6.88 (9H, m, arom), 2.32 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.14 (3H, s, CH_3); ^{13}C NMR (DMSO): δ 200.37, 163.97 and 163.16, 161.60, 137.56, 130.81, 130.01, 129.05, 128.87, 128.18, 128.04, 123.16, 115.36, 103.38, 32.21, 20.52, and 19.30; MS, *m/z* (relative intensity %): 333(M^{+}, 5), 244(20), 216(25), 178(20), 149(18), 135(50), 121(26), 105(100), 91(82), 77(43), 58(70), 51(27). Anal. Calcd. For $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20%. Found: C, 75.30; H, 5.69; N; 3.85%.

5-Benzoyl-4-hydroxy-1-isobutyl-6-methyl-3-phenyl-2(1*H*)-pyridinone (3e). A 0.65 g purple crystals, yield 90%, mp 230–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641 (C=O), 1535 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.80 (1H, broad, OH), 7.58–7.27 (10H, m, arom), 3.51 (2H, d, ^{3}J = 7.00 Hz, CH_2), 2.25 (3H, s, CH_3), 1.88 (1H, m, CH),

0.91 (3H, d, ^3J = 6.00 Hz, CH_3), 0.76 (3H, d, ^3J = 6.00 Hz, CH_3); ^{13}CNMR (DMSO): δ 200.28, 163.21, and 162.50, 159.30, 131.54, 131.06, 130.79, 129.03, 128.90, 128.32, 128.10, 127.26, 116.23, 104.57, 45.59, 32.21, 26.30, 19.80, and 19.79; MS, *m/z* (relative intensity %): 361 (M^+, 7), 346(4), 306(38), 278 (30), 200(20), 189(15), 129(13), 118(18), 105(100), 89(22), 77(90), 63(14), 51(20). Anal. Calcd. For $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. Found: C, 76.08; H, 6.10; N, 3.56%.

5-Benzoyl-1-butyl-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3f). A 0.65 g purple crystals, yield 91%, mp 220–222°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641(C=O), 1515(C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.50 (1H, broad, OH), 7.54–7.26 (10H, m, arom), 2.71 (2H, t, ^3J = 5.10 Hz, CH_2), 2.27 (3H, s, CH_3), 1.52 (2H, m, CH_2), 1.30 (2H, m, CH_2), 0.83 (3H, t, ^3J = 5.00 Hz, CH_3); ^{13}CNMR (DMSO): δ 200.95, 164.88, and 162.03, 158.07, 132.36, 131.94, 130.84, 130.69, 128.78, 128.16, 127.76, 126.76, 117.83, 103.16, 40.33, 32.27, 28.97, 19.14, and 13.45; MS, *m/z* (relative intensity %): 361 (M^+, 4), 346(5), 306(60), 278 (35), 200(18), 189(15), 147(10), 129(10), 118(18), 105(100), 89(20), 77(84), 63(10), 51(20), 43(37), 41(10). Anal. Calcd. For $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. Found: C, 76.13; H, 6.30; N, 3.58%.

5-Acetyl-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3g). A 0.46 g orange crystals, yield 96%, mp 258–260°C (dec.); IR (KBr): 3100–2550 (broad peak, OH), 1741, 1666 (C=O), 1527 (C=C)cm^{-1}; ^{1}H NMR (DMSO): δ 12.90(1H, s, OH), 11.92 (1H, s, NH), 7.40–7.23(5H, m, arom), 2.58 (6H, s, $2CH_3$). ^{13}C NMR (DMSO): δ 203.88, 165.08, and 162.57, 154.73, 133.59, 131.72, 128.28, 127.32, 109.69, 109.48, 33.57, and 21.57; MS, *m/z* (relative intensity %): 243 (M^+, 12), 216(19), 148(35), 118(25), 91(100), 77(35), 65(37), 51(23).

Ethyl 1-butyl-2-methyl-4,6-dioxo-5-phenyl-1,4,5,6-tetrahydro-3-pyridinecarboxylate (5). A 0.28 g yellow crystals, yield 75%, mp 72–74°C. IR (KBr): 1740, 1717 and 1650 (C=O) 1530 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 7.41–7.07 (5H, m, arom), 4.47 (1H, s, malonyl-H on C_5), 4.14 (2H, t, ^3J = 7.00 Hz, OCH_2), 4.06 (2H, t, ^3J = 6.00 Hz, NCH_2), 2.52 (3H, s, CH_3), 1.68 (2H, m, CH_2), 1.42 (2H, quin, ^3J = 6.50 Hz, CH_2), 1.21 (3H, t, ^3J = 5.00 Hz, CH_3), 0.96 (3H, t, ^3J = 5.00 Hz, CH_3); ^{13}C NMR (DMSO): δ 170.46 and 164.87, 164.53, 162.59, 147.05, 129.83, 129.18, 128.69, 128.11, 62.04, 57.00, 45.79, 30.21, 22.68, 19.66, 14.04, and 13.66; MS, *m/z* (relative intensity %): 330 (M+1, 9), 329 (M^+, 35), 314(82), 283(80), 288(35), 227(92), 213(28), 199(25), 128(23), 91(100), 77(15), 67(24). Anal. Calcd. For $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25%. Found: C, 69.03; H, 7.14; N, 4.07%.

Ethyl (*E*)-3-(7-hydroxy-5-oxo-6-phenyl-2,3,4,5-tetra hydro-1*H*-1,4-diazepin-1-yl)-2-butanoate (7). A 0.27 g Yellow crystals, yield 81%, mp 215–216°C. IR (KBr): 3100–2550 (broad peak, OH), 1721, 1655 (C=O), 1530 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.45(1H, s, OH), 8.35 (1H, broad, NH), 7.38–7.26 (5H, m, arom), 4.31 (2H, q, ^3J = 7.50 Hz, OCH_2), 4.19 (1H, s, =CH), 3.65 (4H, m, CH_2), 2.62 (3H, s, CH_3), 1.29 (3H, t, ^3J = 7.50 Hz, CH_3); ^{13}CNMR (DMSO): δ 170.46 and 164.87, 164.53, 162.59, 147.05, 129.83, 129.18, 128.69, 128.11, 62.04, 57.00, 45.79, 30.21, 22.68, 19.66, 14.04, and 13.66; MS, *m/z* (relative intensity%): 330 (M+1, 9), 329(M^+, 35), 314(82), 283(80), 288(35), 227(92), 213(28), 199(25), 128(23), 91(100), 77(15), 67(24). Anal. Calcd. For $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85%. Found: C, 64.23; H, 6.25; N, 8.55%.

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