Studies on the Different Reaction Pathways
between 3-Acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one and Alkylamines

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3-Acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one has been subjected to condensation with a series of primary amines (ethylamine – octylamine) to clarify the proposed mechanism in our previous study. The reactions of the shorter amines of the series (ethylamine – butylamine) yielded unsymmetric pyridinone products, whereas the other amines (pentylamine – octylamine) yielded symmetrical pyridinones. The starting material and the products as well as the intermediates have been subjected to theoretical analysis by quantum chemical calculations at B3LYP/6-31G(d,p) level, which provided supporting data for the experimental findings.

Key Words: Heterocyclic compounds, Pyranones, Pyridinones, Quantum chemical calculations

Introduction

Heterocyclic systems occur in a wide variety of natural and synthetic compounds that are essential to life in various ways.[1-3] Many heterocyclic compounds are biosynthesized by animals and plants, and are biologically active.[4]

Six-membered nitrogen heterocycles are key units in medicinal chemistry and very interesting intermediates in organic synthesis.[5] For example, 4-pyrones that are oxygen containing six-membered heterocycles have been known as precursors for the synthesis of 4(1*H*)-pyridinones for almost a century.[6] The synthesis of 4(1*H*)-pyridinones have attracted considerable research interest from organic chemists due to their various pharmacological effects like being antibacterial,[7] antifungal,[8] anti-malarial,[9] cardiotonic agents,[10] antihypertensive,[11] anti-neoplastic,[12] anti-inflammatory,[13] analgesic,[14] and anti-Parkinson's disease.[15]

Şener *et al.*[16] performed the synthesis 3-acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one (**1a**) and 3,5-dibenzoyl-2,6-diphenyl-4-pyrone (**1b**) and used these pyrone derivatives as precursors for the synthesis of novel pyridinone systems by reacting them with various amines. When pyranone **1a** was reacted with two-fold excess of one of the amines, the final product was alkylimino-4-(1*H*)-pyridinone; however, pyrone **1b** yielded only the alkyl substituted pyridinone derivative (Scheme 1). Thus, they ended up with a conclusion that the reaction must be in two steps in the case of pyranone **1a**, and the first addition is the Michael addition at the methyl substituted position of the central ring.

The aim of the present study was to react pyranone **1a** with a series of primary amines in an equimolar ratio to prove the proposed mechanism.[16] Moreover, the reproducibility of the reaction with longer chain primary alkylamines was examined. The amines range from *n*-ethylamine to *n*-octylamine so that the effect of the alkyl length of the amines on the product has also been investigated. Some structural and physicochemical data about the present systems have been obtained by quantum chemical calculations at the level of B3LYP/6-31G(d,p).
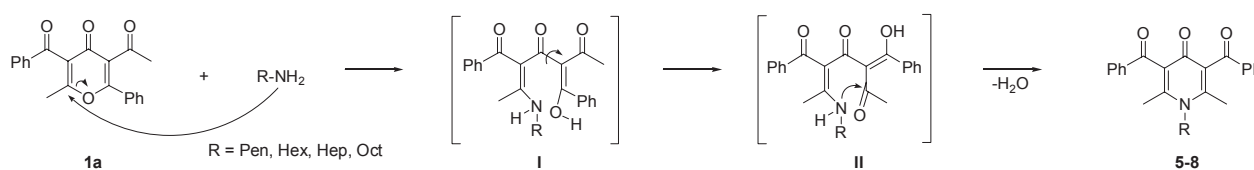
Results and Discussion

The present work involves the investigation of the products of the equimolar condensation reactions of pyranone **1a** with primary amines ranging from ethylamine to octylamine. The summary of the results of the equimolar reactions has been shown in Scheme 2.
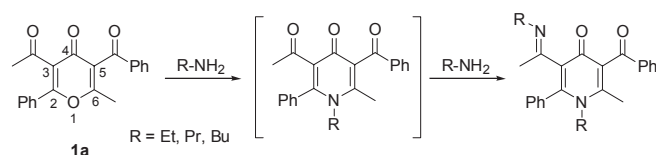
Scheme 1
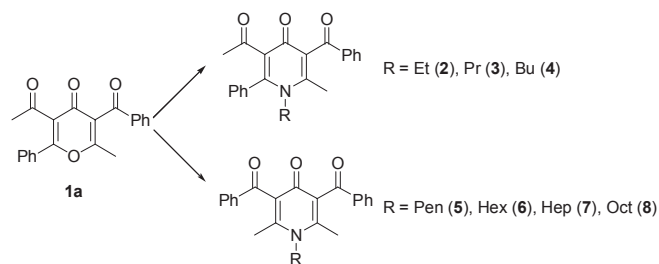
Scheme 2

Scheme 3

The shorter amines (R = Et, Pr, Bu) yielded unsymmetric 3-acetyl-5-benzoyl-6-methyl-1-alkyl-2-phenylpyridin-4(1*H*)-one derivatives of 4-pyridinone, whereas the longer amines (R = Pen, Hex, Hep, Oct) yielded symmetric 3,5-dibenzoyl-2,6-dimethyl-1-alkyl-pyridin-4(1*H*)-one systems. The structure of pentyl pyridinone derivative has been confirmed by crystallographic analysis.[17] This outcome leads the authors to propose the following mechanism (Scheme 3).

The first step of the reaction is the attack of the amine to the sterically less hindered, methyl substituted site (C_6) of the pyranone ring rather than at the phenyl substituted site (C_2). At this point, the length of the amine does not seem to change its nucleophilicity because the calculated Mulliken charges for ethylamine and octylamine are almost equal (−0.04). Therefore, the stability of the addition intermediate should be effective on the determination of the final product. In the case of the longer amine series the stability of the intermediate seems to be enhanced by the rotation of the acetyl moiety (C_3-C_4 single bond). The electronic energies of "not-rotated" **I** and "rotated" **II** of the pentyl derivative **5** are calculated (B3LYP/6-31G(d,p)) to be −1170.362672 and −1170.371339 a.u., respectively. The rotated and not-rotated conformers stand for the conformers rotated and not-rotated around the C_3-C_4 single bond after the amine attack followed by the ring opening, respectively. Therefore, the rotated conformer is favored over the non-rotated one, with 22 kJ/mol energy difference between them. The situation appeared to be opposite in the case of butylamine **4** where the not-rotated conformer **I** was favored over the rotated **II** by a difference of 25 kJ/mol from the calculated energies of −1129.312369 a.u. for **I** and −1129.3024701 a.u. for **II**. Moreover, in order to prove that, the steric hindrance of the amine chain forced the rotation of the C_3-C_4 single bond to end up with the symmetrical product, we compared the relative stability of the intermediates of a branched primary amine, 1,1-diethyl-propylamine. Figure 1 shows the optimized geometries for the corresponding not-rotated (**a**) and rotated conformers (**b**). As seen there, although the distance between the amine and carbonyl moieties is the same (3.12 Å) for the second attack for both cases, the crowded alkyl groups attached to the amine and the phenyl group strongly repel each other and seems to prevent the formation of the final product through the not-rotated conformer (**a**). Thus, the experimetal findings have been supported by the theoretical data. The structures of the synthesized compounds (**2-8**) have been characterized by ^{1}H-NMR, ^{13}C-NMR, and elemental analysis (see experimental part).

The amine can add to the side chain acetyl part of the 4-pyrone derivative. The charges on C_6 and at carbonyl of the acetyl were 0.132 and 0.408 (See Figure 2), respectively which favors the first attack at carbonyl of the acetyl. The attack at the acetyl carbonyl can lead to the formation of the aminal intermediate
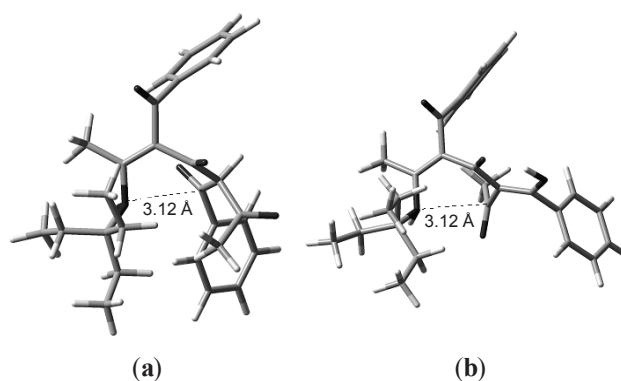

Figure 1. The geometry optimized structures of the not-rotated (**a**) and rotated (**b**) systems when the amine moiety is sterically crowded.
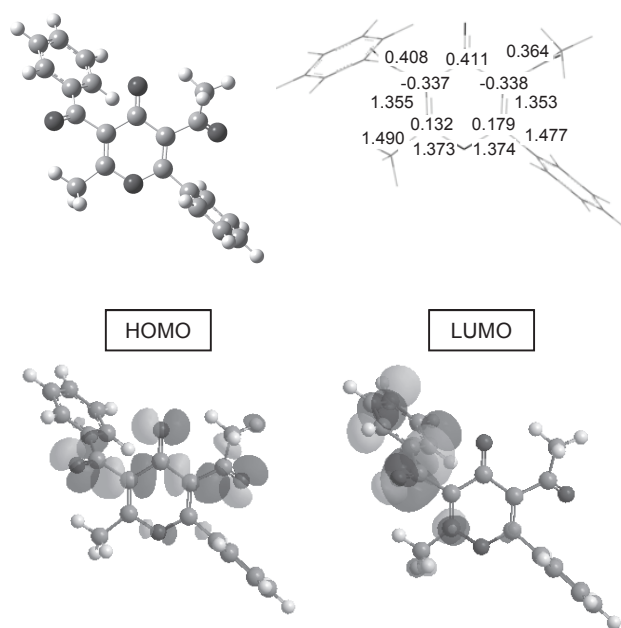

Figure 2. Geometry optimized structure, charges and some structural parameters and the HOMO and LUMO molecular orbital energy schemes of the 4-pyrone derivative.

and a subsequent dehydration process can lead to the corresponding ketimine. The aminal formation proceeds readily but the dehydration step requires a dehydrating agent or high energy. The amine attack at the pyranone ring (C_6) also leads to the aminal, which seems to readily undergo an immediate ring opening to give the intermediate **I** (Scheme 3), which favorably undergoes the second condensation route to form the pyridinone, instead of following a reversible process back to the starting material. Therefore, the pyridinones are the final products under

the given conditions.

The geometry optimized structure together with the HOMO and LUMO molecular orbital energy schemes of the starting 4-pyrone **1a** derivative can be seen in Figure 2. The Mulliken charges on atoms of central importance and some bond lengths have also been reported in the same figure. The phenyl moiety has been found to be almost perpendicular to the central ring so that the steric hindrance due to this big group has been somewhat maximized.

In conclusion, 3-acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one (**1a**) has been reacted with amines to synthesize alkyl pyridinone derivatives. When amines with shorter alkyl chains (C$_4$ or shorter) were used, unsymmetrical pyridinones were obtained; whereas, amines with longer alkyl chains (C$_5$ or longer), symmetrical pyridinones were obtained. This outcome has been explained with a two-step mechanism in which the first addition and ring-opened intermediates undergo the bond rotation around the C$_3$-C$_4$ for the second condensation step to relieve the steric strain. Theoretical calculations at the level of B3LYP/6-31G(d,p) have been carried out for an amine with a branched alkyl chain, which support the suggested explanation.

Experimetal

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a ASR 18 YUICH spectrometer using Si(CH$_4$)$_4$ as the reference. Elemental analyses were performed on a Carlo Erba EAGER 200. Melting points were determined on an Electrothermal Gallenkamp apparatus.

All reagents and solvents were of reagent grade quality and were obtained from commercial suppliers. All solvents were dried by refluxing with appropriate drying agents and distilled before use. The homogeneity of the products was tested in each step by TLC (SiO$_2$).

3-Acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one (1a): Ref 16.

General procedures for pyridinone derivatives (2-8). 3-Acetyl-5-benzoyl-6-methyl-2-phenyl-4*H*-pyran-4-one (**1**) (1 mmol) and amine derivative (1 mmol) were refluxed in ethanol for 24 hours. The solvent was evaporated under reduced pressure to give an oily residue which was treated with ether and finally crystallized from indicated solvent and solvent for each compound: **2**, benzene-cyclohexane; **3**, ethanol:water; **4**, benzene-cyclohexane; **5**, ethanol; **6**, xylene; **7**, benzene-cyclohexane; **8**, ether.

3-Acetyl-5-benzoyl-1-ethyl-6-methyl-2-phenyl-4*H*-pyran-4-one (2): Yield 10.27%; mp 212 °C; ^{1}H NMR (DMSO-d_6) δ 7.819-7.901 (m, 5H, CH, aromatic benzoyl), 7.371-7.645 (m, 5H, CH, ring-phenyl) 1.062-1.098 (t, 3H, *J* = 7.2 Hz, NCH$_2$CH$_3$), 3.747-4.121 (q, 2H, *J* = 7.2 Hz NCH$_2$CH$_3$), 2.27 (s, 3H, CH$_3$-C=O), 2.26 ppm (s, 3H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 173.302 (C=O, C-4), 196.839 (C=O-benzoyl), 201.821 (C=O-acetyl), 128.786-130.246 (ring-phenyl) 132.539-147.316 (benzoyl), 43.335-44.546 (ring-CH$_3$), 32.034 (CH$_2$-NCH$_2$CH$_3$), 15.381 (CH$_3$-NCH$_2$CH$_3$), 17.517-17.547 ppm (CH$_3$-C=O). Anal. Calcd. for C$_{23}$H$_{21}$O$_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.81; H, 5.75; N, 3.90.

3-Acetyl-5-benzoyl-6-methyl-2-phenyl-1-propyl-4(1*H*)-
pyridinone (3): Yield 46.0%; mp 159 °C; ^{1}H NMR (DMSO-d_6) δ 7.508-7.898 (m, 10H, CH, aromatic), 0.542-0.579 (t, 3H, *J* = 7.2 Hz, NCH$_2$CH$_2$-CH$_3$), 1.753-1.784 (m, 2H, NCH$_2$-CH$_2$-CH$_3$), 3.949-3990 (t, 2H, *J* = 7.2 Hz, N-CH$_2$-CH$_2$CH$_3$), 2.26 (s, 3H, CH$_3$-C=O), 2.25 ppm (s, 3H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 173.286 (C=O, C-4), 196.809 (C=O-benzoyl), 201.813 (C=O-acetyl), 134.120-149.247 (ring-phenyl and benzoyl) 128.908-130.104 (double bond), 49.664-50.716 (ring-CH$_3$), 32.048 (CH$_2$-N-CH$_2$-CH$_2$CH$_3$), 22.946 (CH$_2$-NCH$_2$-CH$_2$-CH$_3$), 11.022 (CH$_3$-NCH$_2$CH$_2$-CH$_3$), 17.661 ppm (CH$_3$-C=O). Anal. Calcd. for C$_{24}$H$_{23}$NO$_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.51; H, 6.25; N, 3.75.

3-Acetyl-5-benzoyl-1-butyl-6-methyl-2-phenyl-4(1*H*)-pyridinone (4): Yield 23.3%; mp 153 °C; ^{1}H NMR (DMSO-d_6) δ 7.507-7.899 (m, 10H, CH, aromatic), 0.577-0.613 (t, 3H, *J* = 7.2 Hz, NC$_3$H$_7$-CH$_3$), 0.948-0.984 (m, 2H, NC$_2$H$_5$-CH$_2$-CH$_3$), 1.395-1.753 (m, 2H, NCH$_2$-CH$_2$-C$_2$H$_5$), 3.988-4.029 (t, 2H, *J* = 8-8.4 Hz, N-CH$_2$-C$_3$H$_7$), 2.272 (s, 3H, CH$_3$-C=O), 2.255 ppm (s, 3H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 172.660 (C=O, C-4), 196.809 (C=O-benzoyl), 201.813 (C=O-acetyl), 134.108-147.351 (ring-phenyl and benzoyl) 128.885-129.646 (double bond), 48.091 (ring-CH$_3$), 32.055 (N-CH$_2$-C$_3$H$_7$), 31.465 (NCH$_2$-CH$_2$-C$_2$H$_5$), 19.445 (NC$_2$H$_5$-CH$_2$-CH$_3$), 13.282 (NC$_3$H$_7$-CH$_3$), 17.637 ppm (CH$_3$-C=O). Anal. Calcd. for C$_{24}$H$_{23}$NO$_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.44; H, 6.50; N, 3.58.

3,5-Dibenzoyl-2,6-dimethyl-1-pentyl-4(1*H*)-pyridinone (5): Ref. 16 and Ref. 17.

3,5-Dibenzoyl-2,6-dimethyl-1-hexyl-4(1*H*)-pyridinone (6): Yield 23.0%; mp 177 °C; ^{1}H NMR (DMSO-d_6) δ 7.505-8.033 (m, 10H, CH, aromatic), 0.871-0.904 (t, 3H, *J* = 6.4-6.8 Hz, NC$_5$H$_{10}$-CH$_3$), 1.098-1.345 (m, 4H, NC$_4$H$_8$-CH$_2$-CH$_3$), 1.743-2.103 (m, 4H, NC$_2$H$_4$-CH$_2$-CH$_2$-C$_2$H$_5$), 3.984-4.024 (t, 2H, *J* = 7.6-8.4 Hz, NCH$_2$-CH$_2$-C$_4$H$_9$), 2.267 ppm (s, 6H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 173.279 (C=O, C-4), 196.809 (C=O-benzoyl), 129.118-137.236 (double bond), 48.316, 31.113, 29.457, 26.190, 22.530, 17.647, 14.318 ppm (N-chain and ring-CH$_3$). Anal. Calcd. for C$_{27}$H$_{29}$NO$_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.01; H, 7.01; N, 3.34.

3,5-Dibenzoyl-2,6-dimethyl-1-heptyl-4(1*H*)-pyridinone (7): Yield 24.0%; mp 130 °C; ^{1}H NMR (DMSO-d_6) δ 7.429-8.907 (m, 10H, CH, aromatic), 0.798-0.816 (t, 3H, *J* = 7.2 Hz NC$_6$H$_{12}$-CH$_3$), 0.862-1.497 (m, 8H, NC$_5$H$_{10}$-CH$_2$-CH$_3$), 1.745-1.805 (m, 2H, NC$_2$H$_4$-CH$_2$-CH$_2$-CH$_2$-C$_2$H$_5$), 3.982-4.022 (t, 2H, *J* = 8 Hz, N-CH$_2$-C$_6$H$_{13}$), 2.266 ppm (s, 6H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 173.279 (C=O, C-4), 196.809 (C=O-benzoyl), 128.878-137.206 (double bond), 48.316, 31.670, 29.509, 28.597, 26.491, 22.463, 17.649, 14.402 ppm (N-chain and ring-CH$_3$). Anal. Calcd. for C$_{28}$H$_{31}$NO$_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.21; H, 7.41; N, 3.34.

3,5-Dibenzoyl-2,6-dimethyl-1-octyl-4(1*H*)-pyridinone (8): Yield 15.7%; mp 122 °C; ^{1}H NMR (DMSO-d_6) δ 7.409-8.019 (m, 10H, CH, aromatic), 0.852-0.884 (t, 3H, *J* = 6.4 Hz, NC$_7$H$_{14}$-CH$_3$), 1.021-1.351 (m, 10H, NC$_6$H$_{12}$-CH$_2$-CH$_3$), 1.743-1.810 (m, 2H, NC$_2$H$_4$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-C$_2$H$_5$), 3.980-4.021 (t, 2H, *J* = 8-8.4 Hz, N-CH$_2$-C$_7$H$_{15}$), 2.265 ppm (s, 6H, ring-CH$_3$); ^{13}C NMR (DMSO-d_6) δ 173.280 (C=O, C-4), 196.802 (C=O-benzoyl), 129.128-137.251 (double bond), 48.317, 31.656, 29.506, 29.097, 28.903, 26.536, 22.515, 17.645, 14.410 ppm (N-chain

and ring-CH$_3$). Anal. Calcd. for C$_{29}$H$_{33}$NO$_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.41; H, 7.31; N, 3.24.

Method of theoretical calculation. The initial geometry optimizations of the title pyrone derivative and the pyridinones obtained by the condensation reaction of the starting compound and the primary amines leading to energy minima were achieved by using MM2 method followed by semi-empirical PM3 self-consistent fields molecular orbital (SCF MO) method[18,19] at the restricted level.[20] Then, final geometry optimizations were performed within the framework of density functional theory (DFT, B3LYP)[21,22] at the level of 6-31G(d,p) (restricted closed-shell) without any geometrical restriciton. The exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange.[23] The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional[24] and Lee, Yang, Parr (LYP) correlation correction functional.[25] The BLYP method gives a better improvement over the SCF-HF results. Its predictions are in qualitative agreement with experiment.[26-28] The normal mode analysis for each structure yielded no imaginary frequencies for the 3N-6 vibrational degrees of freedom, where N is the number of atoms in the system. This indicates that the structure of each molecule corresponds to at least a local minimum on the potential energy surface.

All these computations have been performed using Gaussian 03 package programe.[29]

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