NEW β-TRICARBONYL COMPOUNDS: SYNTHESIS, REACTIONS WITH UREA AND SOME THIOUREAS

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Abstract – 2,3-Dihydro-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)furan-2,3-dione 1 reacted with some alkyl carbamates (3a-b) via p,p′-dimethoxydibenzoylketene intermediate 2 giving new β-tricarbonyl compounds (4a-b). Then, these compounds were converted into 1,3-oxazine-2,4(3H)-dione 7 with urea and 2-thioxo-2,3-dihydropyrimidin-4(1H)-ones (6a-c) with some thiourea derivatives, respectively. Pyrimidin-4-ones (6a-c) and oxazine 7 were obtained in good yields. The structures and characterizations of new synthesized compounds were established by the 1H and 13C NMR, IR, UV-VIS spectroscopic data, elemental analysis, and X-ray diffraction method.

INTRODUCTION
The cyclocondensation reaction of 1,3-diones with oxaly chloride represents a convenient synthesis of furan-2,3-dione systems.1 These compounds have been demonstrated to be a versatile, convenient, multifunctional, synthetic building block for the construction of novel heterocyclic starting materials that has in general been widely explored during the last few decades.2 The thermal decomposition of furan-2,3-diones leads to the diacylketene as intermediates which cannot be isolated.3,4 These ketenes are currently of considerable interest, not only because of mechanistic and theoretical considerations,5-8 but also because of their use as synthetic building blocks in organic synthesis.9-11 Recently, 2,3-dihydro-4-(4-
methoxybenzoyl)-5-(4-methoxyphenyl)furan-2,3-dione \( \text{I} \) appeared to be an important starting compound in synthetic organic chemistry.\(^{12-15}\) Also, a convenient preparation of functionalized pyrimidin-2-one, pyrimidinthione and oxazine derivatives from compound \( \text{I} \) and thiosemicarbazones have been reported.\(^{16,17}\)

Pyrimidines generally have been found much interest for their widespread potential biological activities and medicinal applications, thus their chemistry has been investigated extensively.\(^{18,19}\) In particular, various analogues of pyrimidinthiones possess effective antibacterial, antifungal, antiviral, anti-AIDS, insecticidal and miticidal activities.\(^{20,21}\) Furthermore many condensed heterocyclic systems, especially when linked to a pyrimidine ring, play an important role as analgesic, antihypertensive,\(^{22}\) antipyretic, and anti-inflammatory drugs,\(^{23,24}\) also as pesticides, herbicides and plant growth regulators.\(^{25}\) On the other hand, oxazine derivatives have been shown to be antimicrobial agents, fungicides and also exhibit some cytotoxic or as potential anti-tumor agents.\(^{26-28}\) Since pyrimidines and oxazines in general have much more interest for biological and medicinal reasons, above mentioned, we have synthesized new 2-thioxo-2,3-dihydropyrimidin-4(1H)-ones and 1,3-oxazine-2,4(3H)-dione.

**RESULTS AND DISCUSSION**

The starting compound (\( \text{I} \)) was prepared according to literature.\(^{29}\) Since compound \( \text{I} \) readily forms \( p,p' \)-dimethoxydibenzoylketene \( \text{2} \) by thermal ring opening and decarbonylation,\(^{30}\) the formation of the novel \( \beta \)-tricarbonyl compounds (\( \text{4a-b} \)) can be rationalized by nucleophilic addition of the alkyl carbamates (\( \text{3a-b} \)) to reactive intermediate \( \text{2} \). Compound \( \text{I} \) with \( \text{3a-b} \) afforded \( \beta \)-tricarbonyl compounds in boiling toluene in good yields. The formation of \( \text{4a-b} \) were shown briefly in Scheme 1.

![Scheme 1](image)

Previously, the formation of a few \( \beta \)-tricarbonyl compounds, namely 2,2-dibenzoyl-N-alkoxycarbonylacetamides, from 4-benzoyl-5-phenylfuran-2,3-dione and urethanes were determined and
it was shown that β-tricarbonyl compounds were in enol form in solution, whereas keto forms were formed in solid phase. Similarly, in this study, keto-enol tautomers (4, 5) were determined for 4a-b. The relative amounts of keto form of 4a and 4b were found from their $^1$H NMR spectra as 83% and 75%, respectively. In the IR spectra of compound 4a, the carbonyl absorption bands were found to be at about 1672, 1699 and 1754 cm$^{-1}$. Important structural information about 4a was obtained from its $^1$H NMR spectrum. The proton signal of 4a which belongs to the -CH in the keto form was observed at 6.61 ppm. While proton signal of -CO$_2$CH$_3$ group of 4a in the keto form was detected at 3.83 ppm, on the other hand, the proton signal of -CO$_2$CH$_3$ group belonging to 5a in the enol form was determined at 3.79 ppm. The broad peak at 10.62 ppm represents the -NH and the peak at 8.89 ppm is thought to represent the -OH in the enol form. In the $^{13}$C NMR spectrum of 4a, the peaks at 57.55, 57.32 and 55.10 ppm are assigned to the methoxy groups. The peak at 66.31 ppm represents the -CH in the keto form. The formation of pyrimidin-4-ones (6a-c) is outlined briefly in Scheme 2.

![Scheme 2](image)

In the reaction pathway, the formation of intermediate (A) may be initiated by a nucleophilic attack of -NH-R$^2$ on compound 5 to carbonyl group attached to -NHCO$_2$R$^1$ group of 4a-b. By eliminating of -H$_2$NCO$_2$R$^1$ group, the product (A) which cannot be isolated is obtained and the -NH$_2$ group of intermediate A attacks to anisoyl carbonyl on the molecule. Then, intermediate A is cyclized to 6a-c by eliminating H$_2$O. In the $^1$H NMR spectrum of compound 6a has one singlet signal at 9.42 ppm assignable to the -NH band on the pyrimidin-4-one moiety. In the $^{13}$C NMR spectrum of compound 6a carbonyl groups and thiocarbonyl group were observed at 189.42, 158.77 and 174.85 ppm, respectively.

The electronic spectra of the pyrimidin-4-ones (6a-c) recorded in the 200-700 nm region were obtained in DMF solution and their UV spectra were compared with each others. The similarity of UV spectra of 6a and 6b were observed but 6c pattern was determined quite different. The peaks in the UV absorption maxima of 6a, 6b and 6c were observed at 297.0, 298.3 and 283.5 nm, respectively. Methyl group at the compound 6b gives electron as an inductive effect to pyrimidine-4-one cycle. The giving of electron as an
inductive effect is effected to π electron in the cycle. As a result, the energy of π* molecular orbital is decreased and the absorption band of 6b shifts longer to λ_max (298.3 nm). For compounds (6a-c) UV bands with a bathochromic effect resulting from H, Me and Ph attached to N are observed at resulting from the π-π* transition. Also, for compounds 4a and 4b UV bands with a bathochromic effect resulting from the -OMe and -OEt attached to carbonyl were observed at 289.0 and 295.0 nm.

A reasonable proposal for different reaction pathway from 4a-b to 7 is also outlined briefly in Scheme 3. It is assumed that the -NH_2 group of urea attacks to carbonyl group attached to -NHCO_2R group of 4a-b but not the carbonyl group Ar=C=O. Because, -NHCO_2R group can be easily eliminated from 4a-b. The intermediate (A) is also obtained by eliminating of -H_2NCO_2R group. The reaction of 4a-b with urea did not produce to compound 8 via intermediate B. Instead of 8, compound 7 was isolated via intermediate A. When urea and thiourea compounds are compared, the nucleophilic effect of -NH_2 group of urea is less than -NH_2 group of thiourea compounds. For this reason, the formation of compound 8 cannot be occured by attacking -NH_2 group of intermediate A in the enol form. With rearrangament of intermediate A in the enol form, -OH nucleophile attacks to carbonyl group attached to -NH_2 on the molecule. Then, the elimination of ammonia leads to the formation of 1,3-oxazine moiety 7.

The IR spectrum of 7 showed three carbonyl bands 1789, 1692, 1649 cm⁻¹. The ¹H NMR spectrum of 7 showed an -NH absorption band at 8.92 ppm and the ¹³C NMR spectrum of 7 showed three carbonyl carbons at 188.94, 161.26, 146.81 ppm.

The ORTEP of compound 7 shown in Figure 1, the molecule involves two 4-methoxyphenyl rings A (C5-C7) and B (C3-C15) connected to the 1,3-oxazine-2,4-dione ring C (C3-C5, O6). The rings (A, B, and C) are each essentially planar and the dihedral angles, torsion angles, bond lengths and bond angles values of very close analog 1,3-oxazine derivative are in agreement with reported literature values. The dihedral angles between the planes as follows: A/B = 63.85 (9°) A/C =19.10 (16)° B/C = 62.05 (9)°. The molecules in the crystal structure are connected by van der Waals interaction.
**EXPERIMENTAL**

Melting points were determined on an electrothermal 9200 apparatus and are uncorrected. Elemental analysis were carried out using LECO-932 CHNSO analyzer, IR spectra were recorded on a Jasco Plus Model 460 FT IR spectrometer as KBr pellets. The $^1$H and $^{13}$C NMR spectra were acquired from a Gemini-Varian 200 (50) MHz spectrometer (in deuteriochloroform solution containing tetramethyl silane as the internal standard). All experiments were followed by tlc using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm). Electronic spectra of compounds were measured on a Hitachi (150-20) Model UV-VIS spectrometer. For the crystal structure determination, the single-crystal of the compound 7 was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The cylindrically shaped imaging plate covers the two-theta angular range between -60 and 140 ° with a crystal-film distance of 127.4 mm. The graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) and oscillation scans technique with $\Delta\omega = 5$ ° for one image were used for data collection. Images for 7 was taken successfully by varying $\omega$ with three sets of different $\chi$ and $\phi$ values. For each compound the 216 images for six different runs covering about 99.7% of the Ewald spheres were performed. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Crystal Clear (Rigaku/MSC Inc., 2005) software. The structures were solved by the direct method using SHELXS. The positional and atomic displacement parameters (ADPs) were refined by the full-matrix least-squares method using SHELXL and SIR2002.
**Methyl 2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoylcarbamate (4a).** Compound 1 (1.0 g, 2.96 mmol) and methyl carbamate 3a (0.22 g, 2.96 mmol) were refluxed for 3 h in toluene (50 mL). The toluene was evaporated and the remaining oily residue was triturated with anhydrous Et₂O. The white crude product was recrystallized from MeOH and dried on P₂O₅. Mp 165 °C, yield 0.80 g (70%), IR (KBr): ν = 3264 (N-H), 1754, 1699, 1672 cm⁻¹ (C=O). ¹H NMR (200 MHz, CDCl₃): δ = 10.62 (-NH), 8.89 (s, 1H, enol-OH), 7.97-6.57 (m, 8H, Ar-H), 6.61 (s, 1H, keto-CH), 3.83, 3.80, 3.72 ppm (s, 9H, -OCH₃); ¹³C NMR (CDCl₃, 50 MHz): δ = 197.97, 185.72, 172.09 (C=O), 105.07 (enol-CH), 134.23-115.30 (m, Ar-C), 66.31 (keto-CH), 57.55, 57.32, 55.10 ppm (OCH₃). Anal. Calcd for C₂₀H₁₉NO₇: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.54; H, 5.04; N, 3.76.

**Ethyl 2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoylcarbamate (4b).** Compound 1 (1.0 g, 2.96 mmol) and ethyl carbamate 3b (0.26 g, 2.96 mmol) were refluxed for 4 h in toluene (50 mL). The toluene was evaporated and the remaining oily residue was triturated with anhydrous Et₂O. The white crude product was recrystallized from EtOH and dried on P₂O₅. mp 155 °C, yield 0.95 g (81%), IR (KBr): ν = 3265 (N-H), 1752, 1697, 1671 cm⁻¹ (C=O). ¹H NMR (CDCl₃): δ = 10.56 (s, keto-NH), 8.92 (s, enol-OH), 7.26 (s, keto-CH), 4.14 (q, J = 6.9 Hz, 2H, -OCH₂), 3.77, 3.66 (s, 6H, -OCH₃), 1.29, 1.26, 1.22 ppm (t, 3H, -CH₃). ¹³C NMR (CDCl₃, 50 MHz): δ = 196.87, 184.75, 174.02 (C=O), 103.02 (enol-CH), 135.83-117.40 (m, Ar-C), 61.05 (OCH₂) 57.55, 57.32, 55.10 (OCH₃), 15.10 ppm (CH₃). Anal. Calcd for C₂₁H₂₁NO₇: C, 63.15; H, 5.30; N, 3.51. Found: C, 62.94; H, 5.10; N, 3.41.

**5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (6a).** Compound 4a (1.0 g, 2.60 mmol) or compound 4b (1.0 g, 2.50 mmol) and thiourea (0.19 g, 2.50 mmol) were homogeneously mixed. The mixture was heated at 160 °C for 1 h without any solvent in a 50 mL round bottomed flask equipped with a calcium chloride guard tube. After cooling to rt the residue was triturated with anhydrous Et₂O and the crude product recrystallized from EtOH and dried on P₂O₅. Mp 225 °C, yields: 0.65 or 0.78 (71% or 84%), IR (KBr): 3312, 3164 (N-H), 1677, 1661 (C=O), 1605 (C=C), 1467 cm⁻¹ (C=S). ¹H NMR (200 MHz, CDCl₃): δ = 9.42 (N-H), 9.14 (N-H), 7.82-6.83 (m, 8H, Ar-H), 3.87, 3.84 ppm (s, 6H, -OCH₃). ¹³C NMR (50 MHz, CDCl₃): 189.42, 158.77 (C=O), 151.04 (C-CN), 132.09-114.30 (m, Ar-C), 55.78, 55.69 ppm (OCH₃). Anal. Calcd for C₁₉H₁₆N₂O₄S: C, 61.94; H, 4.38; N, 7.60; S, 8.70. Found: C, 61.75; H, 4.15; N, 7.51; S, 8.50.

**5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-3-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (6b).** Compound 4a (1.0 g, 2.60 mmol) or compound 4b (1.0 g, 2.50 mmol) and N-methylthiourea (0.22 g, 2.51 mmol) were homogeneously mixed. The mixture was heated at 160 °C for 1 h without any solvent in a 50
mL round bottomed flask equipped with a calcium chloride guard tube. After cooling to rt the residue was triturated with anhydrous Et₂O and the crude product recrystallized from EtOH and dried on P₂O₅. Mp 285 °C, yields: 0.80 g or 0.76 g (84% or 79%), IR (KBr): 3240 (N-H), 1663, 1644 (C=O), 1598 (C=C), 1492 cm⁻¹ (C=S). ¹H NMR (200 MHz, CDCl₃): δ = 9.63 (N-H), 7.74-6.82 (m, 8H, Ar-H), 3.84, 3.76 (s, 6H, -OCH₃), 3.51 ppm (s, 3H, -CH₃). ¹³C NMR (50 MHz, CDCl₃): 188.95, 157.36 (C=O), 177.14 (C=S), 154.91 (C-NH), 131.99-114.14 (Ar-C), 55.78, 55.56 (OCH₃), 41.08 ppm (N-CH₃). Anal. Calcd for C₂₀H₁₈N₂O₄S: C, 62.81; H, 4.74; N, 7.33; S, 8.38. Found: C, 62.60; H, 4.50; N, 7.10; S, 8.25.

5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-3-phenyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (6c). Compound 4a (1.0 g, 2.60 mmol) or compound 4b (1.0 g, 2.50 mmol) and N-phenylthiourea (0.38 g, 2.50 mmol) were homogeneously mixed. The mixture was heated at 160 °C for 1 h without any solvent in a 50 mL round bottomed flask equipped with a calcium chloride guard tube. After cooling to rt the residue was triturated with anhydrous Et₂O and the crude product recrystallized from EtOH and dried on P₂O₅. Mp 195 °C, yields: 0.67 g or 0.75 g (60% or 68%), IR (KBr): 3204 (N-H), 1680, 1646 (C=O), 1591 (C=C), 1467 cm⁻¹ (C=S). ¹H NMR (200 MHz, CDCl₃): δ = 12.87 (N-H), 7.74-6.36 (m, 13H, Ar-H), 3.76, 3.74 ppm (s, 6H, OCH₃). ¹³C NMR (50 MHz, CDCl₃): 194.23, 158.56 (C=O), 183.07 (C=S), 140.99-117.88 (Ar-C), 60.32, 59.78 ppm (OCH₃). Anal. Calcd for C₂₅H₂₀N₂O₄S: C, 67.55; H, 4.54; N, 6.30. Found: C, 67.28; H, 4.45; N, 6.10; S, 7.10.

5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-2H-1,3-oxazine-2,4(3H)-dione (7). Compound 4a (1.0 g, 2.60 mmol) or compound 4b (1.0 g, 2.50 mmol) and urea (0.15 g, 2.50 mmol) were mixed in 30 mL distilled xylene in a one-necked pear-sahped flask at rt and then refluxed for 5 h. After evaporation of the solvent under reduced pressure, the oily residue was stirred with anhydrous Et₂O. The precipitated crude white product was separated of Et₂O by filtering and recrystallized from EtOH to give 7 as colourless powder, yields: 0.60 g or 0.67 g (65% or 75%), mp 182 °C, IR (KBr): 3204 (N-H), 1789, 1692, 1649 (CO), 1600 cm⁻¹ (C=C). ¹H NMR (200 MHz, CDCl₃): δ = 8.92 (N-H), 7.89-6.80 (Ar-H), 3.84, 3.79 ppm (OCH₃). ¹³C NMR (50 MHz, CDCl₃): 188.94, 161.26, 146.81 (CO), 164.91 (C-O), 132.29-111.25 (Ar-C), 55.84-59.71 ppm (OCH₃). Anal. Calcd for C₁₉H₁₅NO₆: C, 64.59; H, 4.28; N, 7.95. Found: C, 64.50; H, 4.40; N, 7.80.

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REFERENCES AND NOTES