REACTIONS OF β-TRICARBONYL COMPOUND WITH SOME AROMATIC HYDRAZINES AND AMINO ACIDS-ESTERS

Mustafa Saçmacı* and Abdulrezzak Alkan
Department of Chemistry, Bozok University, Arts and Sciences, Yozgat, Turkey
e-mail: msacmaci@hotmail.com

Abstract : Methyl 2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoylcarbamate **1** which is a new β-tricarbonyl compound reacted with some aromatic hydrazines **2a-f** and amino acids-esters **5a-d** to give oxopropanohydrazides **3a-b** and pyrazolones **4c-f** the together with oxopropanoyl-amino acids-esters **6a-d**. These new compounds were obtained in moderate to excellent yields (48-78%). The structures of all new synthesized compounds were determined with the ^{1}H and ^{13}C NMR, IR spectroscopic data and elemental analyses. Most of them were compared with their previously obtained analogues.

Keyword: Tricarbonyl; Cyclocondensation; Pyrazolone; Oxopraponohydrazid; Amino Acid

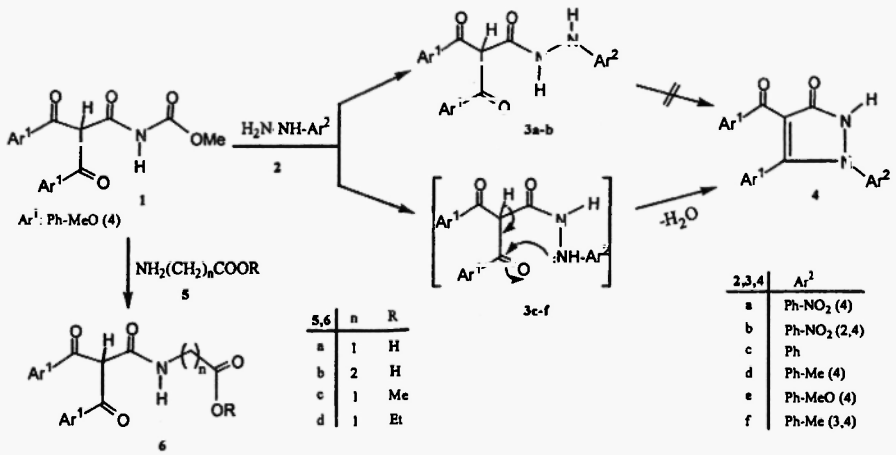
Introduction

In solution, β-ketocarboxylic acids and their derivatives are generally in a solvent and substituent-dependent equilibrium with the corresponding enol tautomers [1-4]. In solid state, only one tautomer-normally the enol form, which is stabilized by either intra or intermolecular hydrogen bonds [3-7] can be observed. Dibenzoylacetic acid derivatives also confirm to these general rules for keto-enol equilibria of β-ketocarboxylic acids: according to NMR spectra, simple dibenzoylacetic acid derivatives prefer the keto form [8] whereas their N-acylamides [9] as well as the N-carboxyalkylamides or dibenzoylacetamides described in ref 10 exist solely at least within the accuracy of NMR measurements as enol tautomers in $CDCl_3$ solution. Surprisingly, however, according to an X-ray structure determination, dibenzoylacetic acid N-carboxymethylamide exists in the solid state as the keto tautomer [10].

Similarly, methyl 2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoylcarbamate **1** was observed to the accuracy of NMR measurement as enol tautomer in $CDCl_3$ solution and the keto tautomer was also determined in solid state. Compound **1** which is obtained from 4-

(4-methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-furandione and methyl carbamate is also a new dibenzoylacetamide derivative [11].

In this paper, the synthesis and characterizations of some oxopropanohydrazides **3a-b**, pyrazolones **4c-f**, oxopropanoylamino acids-esters **6a-d** that were obtained from the reactions between compound **1** with some aromatic hydrazines **2a-f** and amino acids-esters **5a-d** were presented, respectively (Scheme-1). The reactions of **1** with **2a-f** and **5a-d** have not been previously studied, and all the compounds synthesized are original to this study. Among these compounds, the new pyrazolone derivatives might be useful as potential drug compounds. Because, the chemistry of pyrazolone and its derivatives are particularly interesting because of their potential application in medicinal chemistry as analgesic [12,13]. Pyrazolone is an active moiety as a pharmaceutical ingredient, especially in the class of nonstereoidal antiinflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorders [14], and theropeutic agents [15].



Scheme-1 : Reactions and the skeleton of the compounds synthesized

Experimental

Melting points were determined by use of a Buchi melting point apparatus and not corrected. All experiments were followed by tlc using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm). 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 standart). The solvents were evaporated with rotary evaporator Buchi RE model 111. Solvents and other chemical reagents were purchased from Merck and Aldrich. Solvents were distilled before using.

2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-N'-(4-nitrophenyl)-3-oxopropanohydrazid (3a)

Compound **1** (0.50 g, 1.29 mmole) and 4-nitrophenylhydrazine **2a** (0.19 g, 1.29 mmole) were homogeneously mixed. The mixture was heated at 160°C for 1 hour without any solvent in a 50 mL round bottomed flask equipped with a calcium chloride guard tube. After cooling to room temperature the residue was triturated with anhydrous ether and the crude product recrystallized from ethanol. Yield (0.28 g, 48%), mp 209°C. IR (KBr, cm^{-1}): 3310 (N-H), 1689, 1668 (CO), 1599 (C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 9.04, 9.03 (N-H), 8.09-6.34 (Ar-H), 3.89, 3.88 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 188.77 (MeO-Ph-CO), 175.91 (CO-NH), 160.21 (CO-NH), 147.32-112.43 (Ar-C), 63.97 (C-H), 55.93 (OCH_3).

Anal. Calcd. for $C_{24}H_{20}N_2O_7$: C, 64.28; H, 4.50; N, 6.25. Found: C; 64.01, H; 4.30, N, 6.10

2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-N'-(2,4-dinitrophenyl)-3-oxopropanohydrazid (3b)

Compound **1** (0.50 g, 1.29 mmole) and 2,4-dinitrophenylhydrazine **2b** (0.26 g, 1.29 mmole) were homogeneously mixed. The mixture was heated at 160°C for 1 hour without any solvent in a 50 mL round bottomed flask equipped with a calcium chloride guard tube. After cooling to room temperature the residue was triturated with anhydrous ether and the crude product recrystallized from ethanol. Yield (0.35 g, 55%), mp 167°C. IR (KBr, cm^{-1}): 3311 (N-H), 1686, 1620 (CO), 1599 (C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 9.04, 9.03 (N-H), 8.28-6.54 (Ar-H), 3.89 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 188.70 (MeO-Ph-CO), 165.33 (CO-NH), 148.67-113.61 (Ar-C), 63.97 (C-H), 55.97, 55.62 (OCH_3).

Anal. Calcd. for $C_{24}H_{19}N_3O_9$: C, 58.42; H, 3.88; N, 8.52. Found: C; 58.15, H; 3.70, N, 8.35

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (4c)

Compound **1** (0.50 g, 1.29 mmole) was dissolved in 25 mL of xylene and 0.15 mL of phenylhydrazine **2c** (0.12 mL, 1.29 mmole) was dropped in this solution at room temperature and refluxed for 4 h. After evaporation, the oily residue was stirred on a magnetic stirrer with anhydrous ether. The precipitate was separated ether by filtering and recrystallized from distilled ethanol to give product **4c** as a white. Yield (0.39 g, 75%), mp 227°C. IR (KBr, cm^{-1}): 3433 (N-H), 1636, 1615 (CO), 1601 (C=C). ^{1}H-NMR (200 MHz, $CDCl_3$): 9.98 (N-H), 7.28-6.51 (Ar-H), 3.83, 3.81 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 193.74 (MeO-Ph-CO), 160.30 (NH-CO), 144.56 (C-N-Ph), 139.26-113.00 (Ar-C), 105.94 (C-anisoyl cabonyl), 55.56, 55.51 (OCH_3).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C; 72.10, H; 4.95, N, 6.85

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-1-(4-methylphenyl-1,2-dihydro-3*H*-pyrazol-3-one (4d)

Compound **1** (0.50 g, 1.29 mmole) and 4-methylphenylhydrazine hydrochloride **2d** (0.20 g, 1.29 mmole) were refluxed in mixture of 50 mL xylene in the presence of a drop pyridine for 6 h. After solvents were removed by evaporation, the oily residue was triturated with anhydrous ether. The precipitate was separated ether by filtering and recrystallized from distilled ethanol to give product **4d** as a white. Yield (0.38 g, 70%), mp 252°C. IR (KBr, cm^{-1}): 3436 (N-H), 1631, 1600 (CO), 1601 (C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 10.05 (N-H), 7.28-6.51 (Ar-H), 3.83, 3.82 (OCH_3), 2.32 (CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 193.72 (MeO-Ph-CO), 160.23 (NH-CO), 144.43 (C-N-p-toly), 137.90-113.97 (Ar-C), 112.98 (C-anisoyl carbonyl), 55.54, 55.49 (OCH_3), 21.32 (CH_3).

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C; 72.65, H; 5.20, N, 6.50

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-1-(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrazol-3-one (4e)

Compound **1** (0.50 g, 1.29 mmole) and 4-methoxyphenylhydrazine hydrochloride **2e** (0.22 g, 1.29 mmole) were refluxed in mixture of 50 mL xylene in the presence of a drop pyridine for 6 h. After solvents were removed by evaporation, the oily residue was triturated with anhydrous ether. The precipitate was separated ether by filtering and recrystallized from

distilled ethanol to give product **4e** as a white. Yield (0.36 g, 65%), mp 223°C. IR (KBr, cm^{-1}): 3434 (N-H), 1632, 1615 (CO), 1601 (C=C). ^1H NMR (200 MHz, $CDCl_3$): 10.05 (N-H), 7.29-6.51 (Ar-H), 3.82, 3.74, 3.73 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 193.64 (MeO-Ph-CO), 159.07 (NH-CO), 144.48 (C-N-Ph-MeO), 134.43-110.66 (Ar-C), 105.58 (C-anisoyl carbonyl), 55.67, 55.55, 55.48 (OCH_3).

Anal. Calcd. for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C; 69.60, H; 5.25, N, 6.70

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-1-(3,4-dimethylphenyl)-1,2-dihydro-3*H*-pyrazol-3-one (4f)

Compound **1** (0.50 g, 1.29 mmole) and 3,4-dimethylphenylhydrazine hydrochloride **2f** (0.22 g, 1.29 mmole) were refluxed in mixture of 50 mL xylene in the presence of a drop pyridine for 6 h. After solvents were removed by evaporation, the oily residue was triturated with anhydrous ether. The precipitate was separated ether by filtering and recrystallized from distilled ethanol to give product **4f** as a white. Yield (0.33 g, 60%), mp 236°C. IR (KBr, cm^{-1}): 3433 (N-H), 1625, 1615 (CO), 1601 (C=C). ^1H NMR (200 MHz, $CDCl_3$): 10.06 (N-H), 7.28-6.51 (Ar-H), 3.83, 3.71 (OCH_3), 2.21, 2.13 (CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 193.69 (MeO-Ph-CO), 160.21 (NH-CO), 144.38 (C-N-Ph-di-Me), 137.67-112.98 (Ar-C), 105.72 (C-anisoyl carbonyl), 55.53, 55.59 (OCH_3), 19.98, 19.65 (CH_3).

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C; 72.61, H; 5.60, N, 6.70

{[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoyl]amino}acetic acid (6a)

To a boiling solution of compound **1** (0.50 g, 1.29 mmole) in 25 mL xylene, a solution of glycin **5a** (0.09 g, 1.29 mmole) in dry xylene (15 mL) was added and the mixture was refluxed for 3 h. After removal of the solvent, the oily residue was triturated with a mixture of anhydrous ether for 24 h. The white product crystals were filtered off. Yield (0. 29 g, 58%), mp 194°C. IR (KBr, cm^{-1}): 3430 (O-H), 3235 (N-H), 1788, 1694 (C=O). ^1H NMR (200 MHz, $CDCl_3$): 11.36 (N-H and O-H, broad), 8.02-6.96 (Ar-H), 3.83, 3.75 (OCH_3), 1.92 (CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): 189.90 (MeO-Ph-CO), 172.48 (COOH), 162.46 (N-CO), 147.83-114.71 (Ar-C), 112.38 (CH), 56.14, 55.92 (OCH_3), 21.52 (CH_2).

Anal. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.10; H, 4.80 ; N, 3.50

3-{[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoyl]amino}propanoic acid (6b)

To a boiling solution of compound **1** (0.50 g, 1.29 mmole) in 25 mL xylene, a solution of β-alanin **5b** (0.116 g, 1.29 mmole) in dry xylene (15 mL) was added and the mixture was refluxed for 4 h. After removal of the solvent, the oily residue was triturated with a mixture of anhydrous ether for 24 h. The white product crystals were filtered off. Yield (0.34 g, 65%), mp 188°C. IR (KBr, cm^{-1}): 3480 (O-H), 3239 (N-H), 1789, 1693, 1650 (C=O). ^1H NMR (200 MHz, $CDCl_3$): 12.13 (N-H and O-H, broad), 7.84-6.75 (Ar-H), 3.78, 3.71 (OCH_3), 3.52, 3.50, 3.48 ($N-CH_2$), 1.09, 1.07, 1.06 (CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): 184.19 (MeO-Ph-CO), 172.48 (COOH), 164.57 (N-CO), 147.83-114.71 (Ar-C), 112.38 (CH), 56.14, 55.92 (OCH_3), 21.52 (CH_2).

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C; 63.30, H; 5.10, N, 3.30

Methyl {[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoyl]amino}acetate (6c)

To a boiling solution of compound **1** (0.50 g, 1.29 mmole) in 25 mL xylene, a solution of methyl glicinate hydrochloride **5c** (0.16 g, 1.29 mmole) in dry xylene (15 mL) was added and the mixture was refluxed for 3 h. After removal of the solvent, the oily residue was triturated with a mixture of anhydrous ether for 24 h. The white product crystals were filtered off. Yield (0.40 g, 78%), mp 173°C. lR (KBr, cm^{-1}): 3278 (N-H), 1766, 1698, 1671, 1644 (C=O). ^1H NMR (200 MHz, $CDCl_3$): 15.93 (N-H), 8.70-6.60 (Ar-H), 3.97, 3.96 (CH_2), 3.85, 3.71, 3.68 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 191.08 (MeO-Ph-CO), 170.47 (CO-NH), 165.71 (COOMe), 131.17-114.62 (Ar-C), 63.68 (CH), 56.12, 52.26 (OCH_3), 41.38 (CH_2).

Anal. Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C; 63.25, H; 5.20, N, 3.40

Ethyl {[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanoyl]amino}acetate (6d)

To a boiling solution of compound **1** (0.50 g, 1.29 mmole) in 25 mL xylene, a solution of ethyl glicinate hydrochloride **5d** (0.18 g, 1.29 mmole) in dry xylene (15 mL) was added and the mixture was refluxed for 3 h. After removal of the solvent, the oily residue was triturated with a mixture of anhydrous ether for 24 h. The white product crystals were filtered off. Yield

(0.39 g, 72%), mp 165°C. IR (KBr, cm^{-1}): 3269 (N-H), 1760, 1698, 1669, 1643 (C=O). ^1H NMR (200 MHz, $CDCl_3$): 16.04 (N-H), 8.66-6.60 (Ar-H), 4.11, 4.10, 4.08, 4.06 (OCH_2), 3.93 ($N-CH_2$), 3.84, 3.85 (OCH_3), 1.18, 1.16, 1.14 (OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 191.05 (MeO-Ph-CO), 169.96 (CO-NH), 165.63 (COOEt), 131.16-114.62 (Ar-C), 63.67 (CH), 61.00 (CH_2), 56.12 (OCH_3), 41.50 ($NH-CH_2$), 14.48 (CH_3).

Anal. Calcd. for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C; 63.70, H; 5.35, N, 3.25

Result and Discussion

To gain some insight into the chemical behaviour of compound **1** against N-nucleophiles, it was considered of interest to investigate the cyclisation and uncyclisation reactions of **1** with various N-nucleophiles which have aromatic hydrazines and amino acids-esters. In the reaction pathway, the formation of **3a-b** start with a nucleophilic attack of NH_2 group which is included in aromatic hydrazine. Then, methyl carbamate group ($H_2NCOOMe$) is eliminated and it is occured to **3a-b** which can be isolated. When the electron drawing group like nitro attached to phenyl moiety is existed, the cyclisation did not occured and compounds **3c-f** were not obtained under the reaction conditions. Similarly, the formation of pyrazolone derivatives **4c-f** start with a nucleophilic attack of NH_2 group on aromatic hydrazine derivatives **2c-f**. But, when the electron providing group to phenyl moiety like methyl is existed, the cyclisation occured spontanously and compounds **3c-f** were not obtained. In the first step of cyclisation, methyl carbamate group is eliminated and then it is occured to **3c-f** which can not be isolated. In the second step, $NH-Ar^2$ group on the molecule **3c-f** attach to anisoyl carbonyl and compounds **4c-f** are occured by losing H_2O. Previously, analogous reactions have been reported with hydrazines and the corresponding open chain compounds [16,17]. In the IR spectra of compound **4c**, the carbonyl absorption bands are found to be at about, 1636 and 1615 cm^{-1}. Important structural information about **4c** was obtained from its ^1H and ^{13}C NMR spectrum. The ^1H NMR peak of **4c** observed at 9.98 ppm belongs to the -NH and in the ^{13}C NMR spectrum was observed at 193.74 and 160.30 ppm of carbonyl group peaks, respectively.

From this study, it also appeared that compound **1** could not been able to undergo cyclisation reaction amino acids-esters **5a-d**. In the reaction pathway in scheme, a open-chained for the formation of compounds **6a-d** may be initiated by a nucleophilic attack of NH_2 group which is included in amino acid-esters **5a-d** and then methyl carbamate group is eliminated. Also, it appeared that compound **1** could not been able to undergo cyclisation between NH-Ar^2 and anisoyl carbonyl group on compounds **6a-d**.

Acknowledgement

The authors wish to express their gratitude to Prof. Dr. Hasan SEÇEN for helpful and encouraging discussions. This project was financially supported by Erciyes University Research Fund. Project No: FBT-06-43.

References

1. J. Emsley, *Struct. Bonding* **57**, 147 (1984).
2. H. Wengenroth and Meier, *Chem. Ber.* **123**, 1403 (1990).
3. H. S. Bertz and G. Dabbagh, *J. Org. Chem.* **55**, 5161 (1990).
4. C.F.G.C. Geraldes, M. T. Bardos, C.D. Maycock and M. I. Silva, *J. Mol. Struct.* **238**, 335 (1990).
5. G. Gilli, F. Bellucci, V. Ferretti and V. Bertolasi, *J. Am. Chem. Soc.* **111**, 1023 (1989).
6. M. C. Eter, S. M. Reutzel and G. M. Vojta, *J. Mol. Struct.* **237**, 165 (1990).
7. V. Bertolasi, P. Gilli, V. Ferretti and G. Gilli, *J. Am. Chem. Soc.* **113**, 4917 (1991).
8. Y. Akçamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E. M. Peters and H. G. v. Schnering, *Monatsh. Chem.* **117**, 231 (1986).
9. E. Ziegler, G. Kollenz, G. Kriwetz and W. Ott, *Liebigs Ann. Chem*, 1751 (1977).
10. W. M. F. Fabian, G. Kollenz, Y. Akçamur, T. R. Kök, M. Tezcan, M. Akkurt and W. Hiller, *Monatsh. Chem.* **123**, 265 (1992).
11. M. Saçmacı, Ph D Thesis (2002).
12. A. Gürsoy, M. S. Demirayak, G. Çapan, K. Erol, K. Vural, *Eur. J. Med. Chem* **35**, 359 (2000).
13. E. A. M. Badawey, I. M. El-Ashmawey, *Eur. J. Med. Chem.* **33**, 349 (1998).
14. J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J.Kang, E. Hamel, *J. Med. Chem* **33**, 1721 (1990).
15. K. Anzai, M. Furuse, A. Yoshida, A. Matsuyama, T. Moritake, K. Tsuboi, N. Ikota, *J. Radiat. Res.* **45**, 319 (2004).
16. A. N. Kost, 1. 1. Grandberg, *Adv. Heterocyclic. Chem.* **6**, 358 (1966).
17. S. Gelin and M. Chabannet, *Synthesis*, 448 (1978).

Received on June 5, 2007