Synthesis and Reactions of novel 2-arylmethylene-4-oxo-4-[4-methoxy-3-methylphenyl] butanhydrazide derivatives

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Abstract

A novel series of 2-arylmethylene-4-[4-methoxy-3-methylphenyl]-4-oxobutanhydrazide derivatives **(2a-c)** was synthesized *via* the reaction of 3-arylmethylene-5-[4-methoxy-3-methylphenyl]furan-2(3H)-ones (**1a-c)** with hydrazine hydrate. The condensation of the hydrazides (**2a-c**) with various aldehydes gave the corresponding N'-(arylidene)-2-benzylidene-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazides**(3a-i)**

Keywords: perkin reaction,furanone, hydrazide, hydrazone, condensation

1. Introduction

Hydrazides and their derivatives such as hydrazoneshave been used as convenient intermediates for the synthesis of wide variety of nitrogen containing heterocyclic compounds.

Moreover, they exhibit a wide spectrum of biological activities such as anti-inflammatory [**Park, E. B*et al* 2016**], antimalarial [**Gemma *et al* 2006**], antimicrobial [**Sarshira, E*et al* 2016**], antileishmanial [**Visbal*et al* 2008**], anticonvulsant [**Kulandasamy*et al*2009**], antitubercular [**Pavan*et al* 2010**] and antitumor [**Shaker, S. A *et al* 2016**].

Therefore, considering that the hydrazide derivatives are important building blocks for the synthesis of various heterocycles, we have chosen to synthesize a new series of substituted α-[4-methoxy-3-methylbenzoylmethyl] cinnamic acid hydrazides based on the fact that the cinnamoyl moiety has been found in a variety of biologically active substances **[Carvalho*etal* 2008, Sova*et al* 2012 and Bernini *et al* 2007].**

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2. Material and Methods

All melting points reported were uncorrected and determined by the open capillary tube method on a Buuchi 510 melting point apparatus. ^{1}H-NMR spectra were measured on Bruker (200 MHzw) and TMS were used as internal standard, mass spectra were measured on a GC-MSQP 1000EX Schimadzu at Micro analytical Laboratory, Cairo University, Cairo, Egypt, and IR spectra were recorded on a Perking Elmer 1430 ratio recording infrared spectrophotometer with CDS data station using KBr Wafer technique, Ain Shams University, Cairo, Egypt,

2.1.Formation of 3-arylidene-5-[4-methoxy-3-methylphenyl]-2(3*H*)-furanone (1)

To a solution of 5-[4-methoxy-3-methylphenyl]-2(3*H*)-furanone (0.01 mol) and anhydrous sodium acetate (0.01 mol)in acetic anhydride (10ml), the aromatic aldehyde (0.01 mol) namely benzaldehyde, anisaldehydeand/or 4-chlorobenzaldehydewas added. The reaction mixture was heated under reflux for 2hrs, the solid product that separated after cooling was filtered off and crystallized from the proper solvent to give the title products.

3-benzylidene-5-[4-methoxy-3-methylphenyl]-2(3*H*)-furanone(1a), (yield 63%) crystalizedfrom ethanol; m.p 171-173°C; Anal. Calcd. for $C_{19}H_{16}O_3$ (292.23): C, 78.06; H, 5.52. Found: C, 78.31; H, 5.27. IR (KBr, ν, cm^{-1}): 1754 (C=O), 1610(C=C).^{1}H-NMR (DMSO-d_6, δ/ppm): 2.26 (3H, s, CH_3Ar), 3.89 (3H, s, OCH_3), 6.79-7.64 (10H, m, Ar-H and CH olefinic).

3-(4-methoxybenzylidene)-5-[4-methoxy-3-methylphenyl]-2(3*H*)-furanone(1b), (yield 57%) crystalizedfrom ethanol; m.p 182-183°C; Anal. Calcd. for $C_{20}H_{18}O_4$ (322.36): C, 74.52; H, 5.63. Found: C, 74.67; H, 5.39. IR (KBr, ν, cm^{-1}): 1769 (C=O), 1603 (C=C).^{1}H-NMR (DMSO-d_6, δ / ppm): 2.27 (3H, s, CH_3Ar), 3.88 and 3.89 (6H, 2s, 2 OCH_3), 6.77-7.63 (9H, m, Ar-H and CH olefinic)

3-(4-chlorobenzylidene)-5-[4-methoxy-3-methylphenyl]-2(3*H*)-furanone(1c), (yield 76%) crystalizedfrom butanol; m.p 203-205°C; Anal. Calc. for $C_{19}H_{15}ClO_3$ (326.77): C, 69.84; H, 4.63. Found: C, 69.53; H, 4.76. IR (KBr, ν, cm^{-1}): 1782 (C=O), 1594 (C=C). ^{1}H-NMR (DMSO-d_6, δ / ppm): 2.27 (3H, s, CH_3Ar), 3.90 (3H, s, OCH_3), 6.74-7.60 (9H, m, Ar-H and CH olefinic).

2.2.Synthesis of Arylidenehydrazide derivatives

To a solution of (0.01mol) arylidenefuranones (1a-c) in ethanol was added (0.012 mol) hydrazine hydrate at room temperature, the reaction mixture was stirred for 4hrs.The resultant precipitate was filtered off and washed with diluted ethanol.

***2-benzylidene-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide*(2a)**: (yield 90%) crystalizedfrom ethanol, m.p 124^{o}C. Anal. Calc. for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.63; H, 6.03; N, 8.79. IR (KBr, υ, cm^{-1}): 1693, 1651 (CO), 3241 (NH&NH_2). H^1-NMR (DMSO-*d6*, δ ppm): 2.13 (3H, s, CH_3Ar), 3.82(3H, s, OCH_3Ar), 4.35(2H, s, OC-CH_2C=CHPh), 6.50 (H, s, CCHPh), 7.13-7.51(10H, m, Ar-H, *p*-OCH_3Ph-H and NH_2). MS: *m/z*: 324 (5.4%) (M^+).

***2-(4-methoxybenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide* (2b):** (yield 75%) crystalizedfrom ethanol, m.p 144-146^{o}C. Anal. Calc. for $C_{20}H_{22}N_2O_4$ (354.40): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.88; H, 6.41; N, 7.67. IR (KBr, υ, cm^{-1}): 1695, 1647 (CO), 3238, 3335 (NH&NH_2). H^1-NMR (DMSO-*d6*, δ ppm): 2.13 (3H, s, CH_3Ar), 3.76(6H, s, OCH_3 aryl and arylidiene groups), 4.30(2H, s, OC-CH_2C=CHPh), 4.94 (H, s, CCHPh), 7.13-7.51(10H, m, Ar-H, *p*-ClPh-H and NH_2).

***2-(4-chlorobenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide* (2c):** (yield 85%) crystalized from ethanol, m.p 186-187 ^{o}C.Anal. Calc. for $C_{19}H_{19}ClN_2O_3$ (358.82): C, 63.60; H, 5.34; N, 7.81. Found: C, 63.47; H, 5.13; N, 7.98. IR (KBr, υ, cm^{-1}): 1705, 1653. (CO), 3321 (NH&NH_2). H^1-NMR (DMSO-*d6*, δ ppm): 2.12 (3H, s, CH_3Ar), 3.76(3H, s, OCH_3Ar), 4.35(2H, s, OC-CH_2C=CHPh), 6.5 (H, s, CCHPh), 6.87-7.53(10H, m, Ar-H, Ph-H and NH_2).

2.3.Synthesis of hydrazidehydrazonederivatives

To a solution of (0.01 mol) of acid hydrazide derivative (2a-c) in ethanol (20 ml), (0.01 mol) of aromatic aldehydenamely benzaldehyde, salicyaldehydeor 4-chlorobenzaldehydewas added.The reaction mixture was heated under reflux for 4h, after concentration and cooling the product was filtered off and crystallized from a proper solvent to give the corresponding hydrazones.

N',2-dibenzylidene-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide **(3a):** (yield 65%) crystalized from ethanol, m.p 180-181^{o}C.Anal. Calcd. for$C_{26}H_{24}N_2O_3$(412.48): C, 75.71; H, 5.86; N, 6.79.Found:C, 75.49; H, 5.75; N, 6.57. IR (KBr, υ, cm^{-1}): 1682 (CO), 3230 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.12 (3H, s, CH_3Ar), 3.74(3H, s, OCH_3Ar), 6.88 (1H, s, C=CHPh), 7.16-7.621 (14H, m, Ar-H and NH), 8.95 (1H, s, N=CHPh).

2-benzylidene-N'-(4-chlorobenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide **(3b):** (yield 70%) crystalized from ethanol, m.p 198 -199.^{o}C.Anal. Calcd. for$C_{26}H_{23}ClN_2O_3$ (446.93): C, 69.87; H, 5.19; N, 6.27.Found:C, 69.64; H, 5.37; N, 6.03.IR (KBr, υ, cm^{-1}): 1685 (CO), 3239 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.12 (3H, s, CH_3Ar), 3.74(3H, s, OCH_3Ar), 6.86 (1H, s, C=CHPh), 7.16-7.621 (13H, m, Ar-H and NH), 8.97 (1H, s, N=CHPh).). MS: *m/z*: 346 (4.6%) (M^+).

2-benzylidene-N'-(2-hydroxybenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide **(3c):** (yield 70%) crystalized from ethanol, m.p 178-180.^{o}C. Anal. Calcd. for$C_{26}H_{24}N_2O_4$ (428.48): C, 72.88; H, 5.65; N, 6.54.Found:C, 72.61; H, 5.52; N, 6.69. IR (KBr, υ, cm^{-1}): 1696 (CO), 3137 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.19 (3H, s, CH_3Ar), 3.85(3H, s, OCH_3Ar), 6.72 (1H, s, C=CHPh), 6.91-7.87 (13H, m, Ar-H and NH), 9.63 (1H, s, N=CHPh), 10.24 (1H, s, OH).

N'-benzylidene-2-(4-methoxybenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide **(3d):** (yield 65%) crystalized from ethanol, m.p 175-176^{o}C.Anal. Calcd. for$C_{27}H_{26}N_2O_4$ (442.51): C, 73.28; H, 5.92; N, 6.33. Found:C, 73.46; H, 5.77; N, 6.54. IR (KBr, υ, cm^{-1}): 1692 (CO). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.84(3H, s, OCH_3Ar), 3.85(3H, s, *p*-OCH_3Ph), 6.71 (1H, s, C=CHPh), 7.01-7.85 (13H, m, Ar-H and NH), 9.47 (1H, s, N=CHPh).

N'-(4-chlorobenzylidene)-2-(4-methoxybenzylidene)4-(4-methoxy-3-methylphenyl)- -4-oxobutanehydrazide **(3e):** (yield 70%) crystalized from ethanol, m.p 175-176^{o}C.Anal. Calcd. for$C_{27}H_{25}ClN_2O_4$ (476.95): C, 67.99; H, 5.28; N, 5.87. Found:C, 68.11; H, 5.38; N, 5.57. Anal. Calc. for IR (KBr, υ, cm^{-1}): 1693 (CO), 3128 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.84(3H, s, OCH_3Ar), 3.85(3H, s, *p*-OCH_3Ph), 6.72(1H, s, C=CHPh), 7.01-7.86 (12H, m, Ar-H and NH), 9.5 (1H, s, N=CHPh).

***N'-(2-hydroxybenzylidene)-2-(4-methoxybenzylidene)-4-(4-methoxy-3-methylphenyl)- 4-oxobutanehydrazide* (3f):** (yield 50%) crystalized from ethanol, m.p 178-180^{o}C.Anal. Calcd. for$C_{27}H_{26}N_2O_5$ (458.51): C, 70.73; H, 5.72; N, 6.11. Found:C, 70.89; H, 5.46; N, 5.89. IR (KBr, υ, cm^{-1}): 1673 (CO), 3217 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.84(3H, s, OCH_3Ar), 3.86(3H, s, *p*-OCH_3Ph), 6.82(1H, s, C=CHPh), 6.85-7.55 (12H, m, Ar-H and NH), 9.01 (1H, s, N=CHPh), 10.96 (1H, s, OH).

***N'-benzylidene-2-(4-chlorobenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide* (3g):** (yield 70%) crystalized from ethanol, m.p 171-173^{o}C.Anal. Calcd. for$C_{26}H_{23}ClN_2O_3$ (446.93): C, 69.87; H, 5.19; N, 6.27.Found: C, 69.56; H, 5.39; N, 6.51. IR (KBr, υ, cm^{-1}): 1691 (CO), 3246 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.85(3H, s, OCH_3Ar), 6.72 (1H, s, C=CHPh), 7.03-7.9 (13H, m, Ar-H and NH), 9.43 (1H, s, N=CHPh).

***N',2-bis(4-chlorobenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide* (3h):** (yield 70%) crystalized from ethanol, m.p 203-204^{o}C.Anal. Calcd. for$C_{26}H_{22}Cl_2N_2O_3$ (481.37): C, 64.87; H, 4.61; N, 5.82.Found:C, 64.58; H, 4.42; N, 5.93. IR (KBr, υ, cm^{-1}): 1661 (CO), 3234 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.85(3H, s, OCH_3Ar), 5.01 (1H, s, C=CHPh), 6.74-7.9 (12H, m, Ar-H and NH), 9.46 (1H, s, N=CHPh).

***2-(4-chlorobenzylidene)-N'-(2-hydroxybenzylidene)-4-(4-methoxy-3-methylphenyl)-4-oxobutanehydrazide* (3i): (**yield 50%) crystalized from ethanol, m.p 205-206^{o}C.Anal. Calcd. for$C_{26}H_{23}ClN_2O_4$ (462.92): C, 67.46; H, 5.01; N, 6.05. Found: C, 67.71; H, 5.4.87; N, 6.24. IR (KBr, υ, cm^{-1}): 1673 (CO), 3217 (NH). H^{1}-NMR (DMSO-*d6*, δ ppm): 2.2 (3H, s, CH_3Ar), 3.85(3H, s, OCH_3Ar), 6.7(1H, s, C=CHPh), 6.83-7.9 (12H, m, Ar-H and NH), 9.00 (1H, s, N=CHPh), 11.1 (1H, s, OH).

3. Results and Discussion

Hydrazideswere conveniently prepared by the acylation reaction of hydrazines, esters being the most common acylating. In the present work, the synthesis of the starting compounds, 2-arylmethylene-4-oxo-4-[4-methoxy-3-methylphenyl]butanoylhydrazide derivatives (**2a-c)**, was accomplished by the reaction of 5-[4-methoxy-3-methylphenyl]-3-substituted-2(3H)-furanones (**1a-c**) [prepared from the condensation reaction of 5-[4-methoxy-3-methylphenyl]-2(3H)-furanonewith the appropriate aldehydes in the presence of anhydrous sodium acetateunder perkin reaction conditions] with hydrazine hydrate.

The I-R spectra of these compounds **(1a-c)** showed strong absorption bands in the region 1754-1782 cm^{-1} corresponding to the carbonyl group of the furanone ring.

The substituted cinnamoyl hydrazides (**2a-c)** were obtained from the reaction 5-[4-methoxy-3-methylphenyl]-3-substituted-2(3H)-furanones with hydrazine hydrate.

The I-R spectra of these compounds revealed the absence of the absorption bands corresponding to the carbonyl group characteristic of the furanone ring in the region 1740-1770 cm^{-1} and the presence of new absorption bands in the region 3132-3321 cm^{-1} characteristic for NH and NH_2 groups.

We have observed that extensive keto-enol tautomerism exists in compounds **(2a-c)**. The fraction of the enol tautomer in solution is considerably greater because the enol tautomer is stabilized by intramolecular hydrogen bonding and by conjugation of the carbon–carbon double bond with the π-system of the two aromatic rings.

The reactions of the hydrazides (**2a-c**) with the appropriate aromatic aldehydes were carried out in boiling ethanol and led to the formation of the corresponding hydrazones (**3a-i**).

3	Ar	Ar`
a	C_6H_5	C_6H_5
b	C_6H_5	4-ClC_6H_4
c	C_6H_5	2-HOC_6H_4
d	4-$MeOC_6H_4$	C_6H_5
e	4-$MeOC_6H_4$	4-ClC_6H_4
f	4-$MeOC_6H_4$	2-HOC_6H_4
g	4-ClC_6H_4	C_6H_5
h	4-ClC_6H_4	4-ClC_6H_4
i	4-ClC_6H_4	2-HOC_6H_4

The I-R spectra of these compounds revealed the disappearance of the absorption bands attributed to the NH_2 groups and the presence of absorption bands characteristic for the NH groups at 3217-3258 cm^{-1}. The ^{1}H-NMR spectra of these compounds revealed the appearance of new signals in the upfield region (8.95-9.63 ppm) corresponding to the protons of the azomethine groups (C<u>H</u>=N) and the absence of signals characteristic to the NH_2 groups.

The synthesized derivatives were screened for their biological activity against strains of Gram-positive bacteria [such as *Bacillus subtilis*, and *Flavo*], and Gram-negative bacteria [such as *Pseudomonas aeruginosa* and *Entero*].Generally, they exhibited no activity against the tested bacteria.

4. Conclusion

In conclusion, we have synthesized some new 2-arylmethylene-4-[4-methoxy-3-methylphenyl]-4-oxobutanhydrazide derivatives and studied their condensation reaction with various aldehydes. The structures of the newly synthesized derivatives were elucidated by elemental analysis, IR, ^{1}H NMR and in some cases by mass spectrometry.

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تحضير و تفاعلمشتقات 2-أريلميثيلين -4-(4-ميثوكسى-3-ميثيلفينيل)-4-أوكسو بيوتان هيدرازيد الجديدة

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الملخص العربى

تم تحضير سلسلة جديدة من مشتقات 2-أريلميثيلين - 4-(4-ميثوكسى-3-ميثيلفينيل)-4-أوكسو بيوتان هيدرازيد من خلال تفاعل مشتقات الفيورانون المقابلة مع الهيدرازين المائى. تكاثف الهيدرازيدات مع الألدهيدات المختلفة أعطى مشتقات ن-اريليدين-2-اريلميثيلين -4-(4-ميثوكسى-3-ميثيلفينيل)-4-أوكسو بيوتان هيدرازيد المقابلة.