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Products from the Reactions of 4-(4-Methoxybenzoyl)-5-(4-Methoxyphenyl)-2,3-Furandione with Aryl Isocyanates

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4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-furandione (**1**) reacted with aryl isocyanates to give novel pyrrolo[2,3-d] pyrimidines (deazapurines) **2** and 1,3-oxazine-2,4-diones **3** under different conditions. The reaction pathways leading to **2** and **3** include [4 + 2] cycloaddition processes and decarboxylation across the (C=N) bond of the aryl isocyanate accompanied by rearrangements. N1-(1-naphthyl)-2-[2,4-di(4-methoxyphenyl)benzo[h] quinolin-3-yl]-2-oxoacetamide (**4**) was obtained from the thermolysis of **2d**. The formation of **4** proceeded *via* the iminobenzylfurandione as probable intermediate. The synthesis of new examples 1,3-oxazine-2,4-diones and pyrrolo[2,3d]pyrimidines following the unknown procedure and subsequent reactions using **1** and different aryl isocyanates has been reported.

Key Words: Pyrrolo[2,3-d]pyrimidines, 1,3-Oxazines, 2-Oxoacetamide, [4 + 2] Cycloaddition.

INTRODUCTION

Pyrrolo[2,3-d]pyrimidines (7-deazapurines) are an important class of compounds, structurally and chemically related to nucleosides and some antibiotics[1]. The well known biological activity of these compounds has led to intensive investigation of their use as antitumor, anti-allergic, anti-viral and anti-inflammatory agents[2]. Fused 1,3-oxazine-2,4-diones have also been evaluated as cytotoxic or as potential anti-tumor agents[3]. Due to the interest in this class of compounds, we have previously reported[7] the reactivity and synthetic applications of these compounds.

4-Aryl substituted heterocyclic 2,3-diones, such as furandiones are versatile starting materials for a variety of reactions *via* generated cycloaddition of heterocumulenes across the oxa-1,3-diene subunit of α-oxoketenes by thermolysis as well as addition of nucleophiles leading to a number of mono- and bicyclic heterocyclic systems[4]. The oxa-1,3-diene moiety in 4-benzoyl-5-phenylfuran-2,3-dione is well known to add isocyanides[5, 6] and several heterocumulenes *via* formal [4 + 1] or [4 + 2] cycloaddition processes affording various novel heterocyclic

systems. The oxa-1,3-diene system in 4-benzyl substituted five-membered heterocyclic 2,3-diones by the benzoyl group and the endocyclic C=C double bond is capable to add isocyanides, isocyanates, carbodiimides and ketenimines leading to various bicyclic heterocycles, and furan-2,3-diones are in general considered as convenient and versatile synthons in heterocyclic synthesis. They can serve as heterodienes in various cycloaddition processes, usually accompanied by surprising rearrangements[7–9]. Furthermore, these molecules are suitable precursors in generating highly reactive α-oxoketenes during simple thermolysis in solution[10, 11].

EXPERIMENTAL

Melting points were obtained on an Electrothermal 9200 apparatus and not corrected. The FT-IR spectra were measured on a Jasco Plus Model 460 spectrometer, as potassium bromide pellets. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Gemini-Varian 200 MHz spectrometer using tetramethylsilane as an internal standard. Elemental analyses were carried out by a Carlo-Erba 1108 Model 105 microanalyzer.

General Procedure for the synthesis of 1*H*-pyrrolo[2,3d]pyrimidine-2,5,6-triones

1.0 g (2.96 mmol) of **1** were added to excess of (8.88 mmol) aryl isocyanates in a 25 mL round-bottomed flask equipped with a calcium chloride tube. The mixture was heated at 65°C for 24 h. After cooling to roomtemperature, the residue was triturated with anhydrous ether, and the crude product was recrystallized from corresponding solvents and dried on P_2O_5.

4,7a-Di(4-methoxyphenyl)-1,3,7-triphenyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3d]pyrimidine-2,5,6-trione (2a)

Compound **2a** was prepared **1** and 1.050 g phenyl isocyanate. IR (cm^{-1}) (KBr): 1730, 1686, 1674 ν(C=O), 1579 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 7.67–6.20 (m, 23H, Ph), 3.89, 3.76 (s, 6H, CH_3O); ^{13}C-NMR ($CDCl_3$): δ 178.35, 165.37, 164.59 (C=O), 162.469–115.58 (C=C, arom. and aliph.), 81.36 (N—C—N), 57.53, 57.28 (CH_3O).

4,7a-Di(4-methoxyphenyl)-1,3,7-tri(4-methylphenyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6-trione (2b)

Compound **2b** was prepared **1** and 1.180 g *p*-tolyl isocyanate. IR (cm^{-1}) (KBr): 1727, 1709, 1684 ν(C=O), 1586 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 7.64–6.04 (m, 20H, Ph), 3.88, 3.77 (s, 6H, CH_3O), 2.25, 2.18, 2.15 (s, 9H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 178.51, 165.58, 164.47 (C=O), 162.35–115.52 (C=C, arom. and aliph.), 81.36 (N—C—N), 57.50, 57.28 (CH_3O), 23.00, 22.94, 22.92 (CH_3).

1,3,7-Tri(4-chlorophenyl)-4,7a-di(4-methoxyphenyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6-trione (2c)

Compound **2c** was prepared **1** and 1.360 g 4-chlorophenyl isocyanate. IR

(cm^{-1}) (KBr): 1737, 1711, 1684 ν(C=O), 1584 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 7.58–6.23 (m, 20H, Ph), 3.89, 3.79 (s, 6H, OCH_3); ^{13}C-NMR ($CDCl_3$): δ 177.789, 164.919, 164.849 (C=O), 162.705–115.82 (C=C, arom. and aliph.), 81.49 (N—C—N), 57.56, 57.36 (CH_3O).

4,7a-Di(4-methoxyphenyl)-1,7-di(1-naphthyl)-3-(2-naphthyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6-trione (2d)

Compound **2d** was prepared **1** and 1.5 g 1-naphthyl isocyanate. IR (cm^{-1}) (KBr): 1750, 1711, 1689 ν(C=O), 1593 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 8.12-6.08 (m, 17H, Ph), 3.92, 3.67 (s, 6H, CH_3O); ^{13}C-NMR ($CDCl_3$): δ 178.757, 165.139, 164.050 (C=O), 162.335–115.06 (C=C, arom. and aliph.), 82.87 (N—C—N), 57.69, 57.14 (CH_3O).

1,3,7,7a-Penta(4-methoxyphenyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3-d]-pyrimidine-2,5,6-trione (2e)

Compound **2e** was prepared **1** and 1.320 g 4-methoxyphenyl isocyanate. IR (cm^{-1}) (KBr): 1729, 1712, 1682 ν(C=O), 1579 ν (C=C). ^{1}H-NMR ($CDCl_3$): δ 7.63–6.10 (m, 20H, Ph), 3.88, 3.65 (s, 15H, CH_3O); ^{13}C-NMR ($CDCl_3$): δ 178.519, 165.706, 164.449 (C=O), 162.402–115.43 (C=C, arom. and aliph.), 81.27 (N—C—N), 57.501, 57.453, 57.273 (CH_3O).

1,3,7-Tri(3,5-dimethylphenyl)-4,7a-di(4-methoxyphenyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6-trione (2f)

Compound **2f** was prepared **1** and 1.300 g 3,5-dimethylphenyl isocyanate. IR (cm^{-1}) (KBr): 1732, 1705, 1665 ν(C=O), 1587 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 7.64–5.81 (m, 17H, Ph), 3.88, 3.77 (s, 6H, CH_3O), 2.06, 1.94 (s, 18H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 178.577, 165.479, 164.549 (C=O), 162.453–115.50 (C=C, arom. and aliph.), 81.36 (N—C—N), 57.562, 57.253 (CH_3O), 22.894 (CH_3).

General Procedure for the synthesis of 2H-1,3-oxazine-2,4-diones

A mixture of 1.0 g (2.96 mmol) **1** and 2.96 mmol phenyl isocyanate was heated at 120°C until the evolution of CO has subsided (1 h). The cooled reaction mixture was triturated with dry ether and then recrystallized from corresponding solvents and dried on P_2O_5.

5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-3-phenyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (3a)

Compound **3a** was prepared **1** and 0.350 g phenyl isocyanate. IR (cm^{-1}) (KBr): 1774, 1690, 1646 ν(C=O). ^{1}H-NMR ($CDCl_3$): δ 7.95–6.81 (m, 13H, Ph), 3.84, 3.79 (s, 6H, CH_3O); ^{13}C-NMR ($CDCl_3$): δ 190.799, 166.598, 165.035 (C=O), 162.364–113.47 (arom. and aliph. C=C), 57.52, 57.44 (CH_3O).

5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-3-(4-methylphenyl)3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (3b)

Compound **3b** was prepared **1** and 0.39 g *p*-tolyl isocyanate. IR (cm^{-1}) (KBr):

1773, 1688, 1660 ν(C=O), ^{1}H-NMR ($CDCl_3$): δ 7.95–6.80 (m, 12H, Ph), 3.81, 3.76 (s, 6H, CH_3O), 2.38 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 190.719, 166.579, 165.014 (C=O), 162.406–113.70 (arom and aliph. C=C), 57.46, 57.38 (CH_3O).

3-(4-Chlorophenyl)-5-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-3,4-dihydro2*H*-1,3-oxazine-2,4-dione (3c)

Compound **3c** was prepared **1** and 0.45 g 4-chlorophenyl isocyanate. IR (cm^{-1}) (KBr): 1769, 1690, 1654 ν(C=O), 1598 ν(C=C). ^{1}H-NMR ($CDCl_3$): δ 7.95–6.78 (m, 12H, Ph), 3.82, 378 (s, 6H, CH_3O); ^{13}C-NMR ($CDCl_3$): δ 190.68, 166.65, 165.07, 162.469–113.33 (m, arom. C=C), 57.55, 57.44 (CH_3O).

5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)-3-phenyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (3d)

Compound **3d** was prepared **1** and 0.50 g 1-naphthyl isocyanate. IR (cm^{-1}) (KBr): 1770, 1682, 1659 ν(C=O). ^{1}H-NMR (DMSO): δ 8.20–7.02 (m, 11H, Ph), 3.86, 3.81 (s, 6H, CH_3O); ^{13}C-NMR (DMSO): δ 190.72, 166.02, 164.03 (C=O), 162.797–113.65 (m, arom. C=C), 57.52, 57.44 (CH_3O).

N1-(l-Naphthyl)-2-[2,4-di(4-methoxyphenyl)benzo[h]quinolin-3y1]-2-oxoactamide (4)

4,7a-Di(4-methoxyphenyl)-1,7-di(1-naphthyl)-3-(2-naphthyl)-2,3,5,6,7,7a-h exahydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6-trione 1.0 g (1.32 mmol) was kept in an oil-bath at 220°C for 30 min, then the melted product was dissolved in ether/petrol ether (1 : 1), and stirred for a few days at room temperature. The red crude product was filtered and then dried on a P_2O_5. IR (KBr): ν 3233 (N—H), 1748, 1704 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 8.22–6.04 (m, 11H, arom), 3.95, 3.48 (s, 6H, CH_3O), NH (no detection); ^{13}C-NMR ($CDCl_3$): δ 182.702, 171.487 (C=O), 164.608–115.00 (C=C), 57.45, 56.93 (CH_3O).

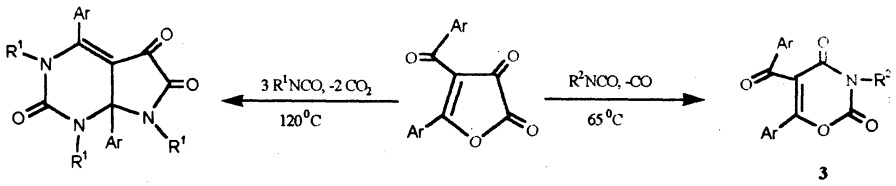
RESULTS AND DISCUSSION

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-furandione **(1)** reacted with some aryl isocyanates in neat about 24 h at 65°C, releasing two moles of carbon dioxide, led to the formation of the compounds **(2a–f)** in 70–80% yield **(Scheme-1)**. All the reaction steps obviously include formal [4 + 1] or [4 + 2] cyclo-addition processes accompanied by long-range Dimroth furandione rearrangements[12]. Previously, the mechanism of formation of pyrrolo-[2,3-d]pyrimidines from the furandione with aryl isocyanates was reported[12]. Compound **2a** shows characteristic IR absorption band at 1730, 1686, 1674 cm^{-1} (C=O). Its characteristic ^{13}C-NMR signals at 178.35, 165.37, 164.59 ppm (C=O), 81.36 ppm (N—C—N), are in full agreement with its proposed structures (Table-1).

TABLE-1
PHYSICAL DATA AND ELEMENTAL ANALYSES OF COMPOUNDS **2** AND **3**

Compds.	Yield (%)	m.p. (°C) (solvent)	m.f. (m.w.)	Elemental analysis (%), Calcd./(Found)		
				C	H	N
2a	70	201 (acetic acid)	$C_{38}H_{29}N_3O_5$ (607)	75.12 (74.85)	4.77 (4.83)	6.91 (7.01)
2b	65	225 (ethanol)	$C_{40}H_{35}N_3O_5$ (637)	75.80 (76.02)	5.39 (5.69)	6.47 (6.22)
2c	75	235 (ethanol)	$C_{38}H_{26}N_3O_5Cl_3$ (710)	64.18 (63.98)	3.66 (3.40)	5.91 (5.60)
2d	80	217 (butanol)	$C_{50}H_{35}N_3O_5$ (757)	79.20 (79.46)	4.62 (4.94)	5.54 (5.97)
2e	65	222 (butanol)	$C_{41}H_{35}N_3O_8$ (697)	70.58 (70.86)	5.02 (4.94)	6.02 (5.97)
2f	60	219 (ethanol)	$C_{44}H_{41}N_3O_5$ (691)	76.40 (76.15)	5.93 (5.90)	6.07 (6.01)
3a	75	232 (butanol)	$C_{25}H_{19}NO_6$ (429)	69.93 (69.80)	4.42 (4.51)	3.26 (3.14)
3b	65	195 (methanol)	$C_{26}H_{21}NO_6$ (443)	70.42 (70.18)	4.74 (4.51)	3.16 (2.93)
3c	55	220 (acetic acid)	$C_{25}H_{18}NO_6Cl$ (463)	64.72 (64.62)	3.88 (3.86)	3.02 (2.83)
3d	60	289 (acetic acid)	$C_{29}H_{21}NO_6$ (479)	72.65 (72.76)	4.38 (4.38)	2.92 (2.89)
4	80	225 (acetone)	$C_{39}H_{30}N_2O_4$ (590)	79.32 (79.06)	5.08 (4.81)	4.74 (5.01)

The thermal decomposition of 4-benzoyl-5-phenylfuran-2,3-dione leads to the dibenzoylketene as an intermediate which undergoes cycloaddition reactions with hetero-cumulenes[13]. In a similar way, the thermal decomposition of novel 4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-furandione generates to the intermediate *p,p'*-dimethoxy dibenzoylketene[14]. The 1,3-oxazine-2,4-diones **(3a–d)** were obtained in 40–70% yields by the addition of aryl isocyanates to the α-oxoketene generated by thermolysis of **1** (**Scheme-1**). The structures of compounds **(3a–d)** were confirmed by elemental analysis, IR, ^1H and ^{13}C-NMR spectral data, *e.g.*, three carbonyl absorption bands 1774, 1690, 1646 cm^{-1} (C=O) in the IR spectra as well as the corresponding signals in the ^{13}C-NMR spectra at δ 190.80 (anisoyl C=O), 165.03 (N—C=O), 166.58 (anisyl —C—O), 149.70 (N—CO—O), similar to very close analogues[15].

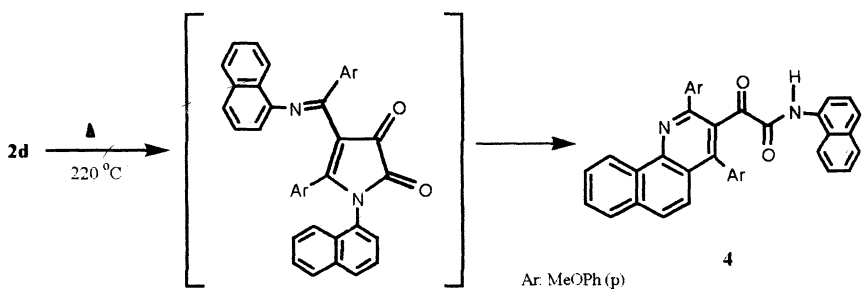


2,3	R^1	R^2
a	C_6H_5	C_6H_5
b	$C_6H_4CH_3$-(4)	$C_6H_4CH_3$-(4)
c	C_6H_4Cl-(4)	C_6H_4Cl-(4)
d	$C_{10}H_7$	$C_{10}H_7$
e	$C_6H_4OCH_3$-(4)	-
f	$C_6H_3(CH_3)_2$-(3,5)	-

Ar: MeOPh (p)

Scheme-1

Finally, from thermolyze of **2d** at 220°C, compound **4** was furnished (**Scheme 2**). The product **4** was gained in 40% yield. It proceeded *via* iminobenzyl-furandiones as probable intermediate similar to the mechanism of thermolyze reaction of 7,7a-dihydro-1,3,4,7,7a-pentaphenyl-1*H*-pyrrolo[2,3-d]pyrimidine-2,5,6(3*H*)-trione to N,2,4-triphenyl-3-quinolin glyoxylamide[7]. In the IR spectrum of compound **4**, the (C=O) absorption bands were observed at 1748 and 1704 cm^{-1}. The NH absorption band could not be identified in the ^{1}H-NMR spectrum of **4**, because of intramolecular hydrogen bonding between NH and oxygen at the 2-position[16]. That compound can be regarded as simple [4 + 2]-cycloreversion and this combined reaction sequence represents one example of the Ziegler-Hafner azulene synthesis[17].



Scheme-2

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