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SYNTHESIS OF 5, 7-DIARYL-1,5-DIHYDRO (OR 1, 2, 3, 5-TETRAHYDRO)-PYRANO[2, 3-*d*] PYRIMIDIN-2, 4-DIONES (OR 2-THIOXO-4-ONES).

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Abstract

Some 5, 7-diaryl-1,5-dihydro (or 1, 2, 3, 5-tetrahydro)- pyrano[2, 3-*d*] pyrimidin-2, 4-diones (or 2-thioxo-4-ones) (**3a-g**) has been synthesized in one-step by the cyclocondensation of barbituric acid or thiobarbituric acid (**1**) with arylideneacetophenones (**2a-d**), in glacial acetic acid in the presence of phosphorous pentoxide. The structures of the compounds **3a-g** were determined by their UV, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.

Introduction

There has been a continued interest in the synthesis of pyranopyrimidines because of the pharmacological activities[1-4] associated with this system. Although a variety of routes[5-8] for the synthesis of these compounds have been described, the majority of them involve a number of steps and the yields are relatively poor. Therefore, it is felt necessary to develop an efficient method for the synthesis of these compounds in better yields. There is a report[9] on the reactions of barbituric acids with α,β-unsaturated carbonyl systems.

In continuation to our previous work[10,11] on the synthesis of 5,7-diaryl-1,5-dihydropyrano[2,3-*d*]pyrimidin-2,4-diones, we report herein syntheses of 5,7-di-*p*-tolyl-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione **3a**, 2-thioxo-5,7-di-*p*-tolyl-1,2,3,5-tetrahydro-pyrano[2,3-*d*]pyrimidin-4-one **3b**, 7-(*p*-methoxy-phenyl)-5-*p*-tolyl-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione **3c**, 7-(*p*-methoxy-phenyl)-2-thioxo-5-*p*-tolyl-1,2,3,5-tetrahydro-pyrano[2,3-*d*]pyrimidin-4-one **3d**, 7-(*p*-chloro-phenyl)-5-*p*-tolyl-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione **3e**, 7-(*p*-chloro-phenyl)-2-thioxo-5-*p*-tolyl-1,2,3,5-tetrahydro-pyrano[2,3-*d*]pyrimidin-4-one **3f** and 7-biphenyl-4-yl-5-(*p*-methoxy-phenyl)-2-thioxo-1,2,3,5-tetrahydro-pyrano[2,3-*d*]pyrimidin-4-one **3g** by selecting a number of arylideneacetophenones (**2a-d**) as the α,β-unsaturated carbonyl system having different substituents on the aromatic rings for reaction with barbituric acid or thiobarbituric acid (**1**) as the active methylene component. Compounds **3a-g** were characterized by different spectroscopic methods and elemental analyses.

The formation of compounds **3a-g** may be explained by the initial formation of a 1:1 adduct (**A**) followed by cyclocondensation (**Scheme 1**). The formation of such an adduct has been reported[12] in the literature.

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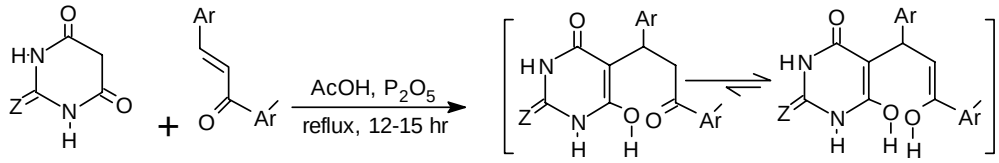
Scheme-1



1 **2**

	Z	Ar	Ar´
2a, **3**a	O	4-$CH_3C_6H_5$	4-$CH_3C_6H_5$
2a, **3**b	S	4-$CH_3C_6H_5$	4-$CH_3C_6H_4$
2b, **3**c	O	4-$CH_3C_6H_5$	4-$CH_3OC_6H_4$
2b, **3**d	S	4-$CH_3C_6H_5$	4-$CH_3OC_6H_4$
2c, **3**e	O	4-$CH_3C_6H_5$	4-ClC_6H_4
2c, **3**f	S	4-$CH_3C_6H_5$	4-ClC_6H_4
2d, **3**g	S	4-$CH_3OC_6H_5$	4-$C_6H_5C_6H_4$

A $-H_2O$

3

Experimental

The UV spectra were run in methanol using SHIMADZU UV-160A ultraviolet spectrophotometer. Melting points are uncorrected. The IR spectra were recorded as KBr pellet using SHIMADZU IR-470 infra-red spectrophotometer in the range of 4000-400 cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded on a JEOL-400 MHz NMR spectrometer. The solvents used were d_6- DMSO and $CDCl_3$, TMS being the reference. All the compounds gave expected C, H and N analyses.

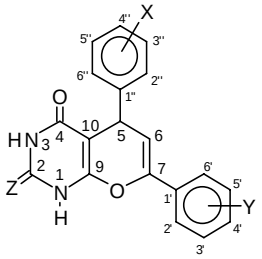
1,3-Di-*p*-tolyl-propenone **2a**, 1-(*p*-methoxy-phenyl)-3-*p*-tolyl-propenone **2b,** 1-(*p*-chloro-phenyl)-3-*p*-tolyl-propenone **2c** and 1-biphenyl-4-yl-3-(*p*-methoxy-phenyl)-propenone **2d** were prepared from the reactions of corresponding substituted aldehydes and substituted acetophenones by following primarily literature method[13] with modification of the reaction conditions wherever necessary. The reactions described in the present paper were carried out following a general procedure.[9]

*General Procedure***:** A mixture of arylideneacetophenone (0.005 mol) and barbituric acid or thiobarbituric acid (0.005 mol) were dissolved in acetic acid (10mL) and P_2O_5 (2g) in a round-bottomed flask equipped with a magnetic stirrer, a refluxing condenser and a drying tube. The reaction mixture was refluxed at 135-140°C for 6-11 hours and the

course of the reaction was followed by TLC on silica gel plates (eluting solvent; EtOAc). The mixture was allowed to cool and treated with crushed ice. The solid, thus obtained, was filtered off, washed with cooled water, dried and purified by recrystalization from rectified spirit.

Results and Discussion

Compounds **3a-g** were synthesized from **1** and the corresponding **2a-d** in presence of glacial acetic acid and P_2O_5 under refluxing conditions in an analogous manner reported[9] previously. The assignment to the structures of the compounds **3a-g** was made on the basis of their UV, IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses.



3a-g

Substituent	3a	3b	3c	3d	3e	3f	3g
X	4-CH_3	4-CH_3	4-CH_3	4-CH_3	4-CH_3	4-CH_3	4-OCH_3
Y	4-CH_3	4-CH_3	4-OCH_3	4-OCH_3	4-Cl	4-Cl	4-C_6H_5
Z	O	S	O	S	O	S	S

The observed λ_{max} values of compounds **3a-g** agree well to the expected values in their UV spectra. The absorption bands in the range 402-282 nm may be assigned to the $\pi\rightarrow\pi^*$ of C=O in these compounds. The weak $n\rightarrow\pi^*$ absorption bands in the cases of these compounds due to C=O were probably masked within the $\pi\rightarrow\pi^*$ absorption range of 402-282 nm.

The IR data of the compounds **3a-g** (Table-2) showed sharp as well as broad bands in the range (ν_{max}) 3450-3350 cm^{-1} indicating the presence of N-H group. The absorption bands at 1700-1650 cm^{-1} indicate the presence of non-conjugated C=O stretching (C-2) including the barbituric acid moieties.[14] The bands at 1630-1500 cm^{-1} were assigned to C=O (C-4), C=C of aromatic rings and C=N of the conjugated form of barbituric acid part. Additional bands were observed at 1445-660 cm^{-1} due to these structural units.[14]

Table 1. Reaction conditions and analytical data of the compounds 3a-f.

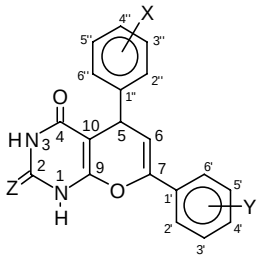
Compound	Reflux time (hr)	Reaction temp.(^{0}C)	% C Found (Calcd)	% H Found (Calcd)	%N Found (Calcd)	Mol. formula	MS (m/z)
3a	06-07	135-140	71.36 (70.80)	5.20 (5.20)	7.71 (8.09)	$C_{21}H_{18}N_2O_3$	346.20
3b	09-10	135-140	68.85 (69.61)	5.01 (4.97)	7.47 (7.70)	$C_{21}H_{18}N_2O_2S$	362.20,
3c	10-11	135-138	69.02 (69.61)	5.04 (4.97)	7.32 (7.73)	$C_{21}H_{18}N_2O_4$	362.20
3d	08-09	132-136	57.81 (66.66)	4.59 (4.76)	6.42 (7.41)	$C_{21}H_{18}N_2O_3S$	378.15
3e	10-11	135-140	65.11 (65.50)	4.16 (4.09)	7.57 (7.64)	$C_{20}H_{15}N_2O_3Cl$	366.11
3f	09-10	136-140	61.91 (62.75)	4.10 (3.92)	7.11 (7.31)	$C_{20}H_{15}N_2O_2ClS$	382.09
3g	07-08	136-140	68.87 (70.91)	4.60 (4.54)	6.20 (6.36)	$C_{26}H_{20}N_2O_3S$	440.20

Table 2. Physical constants, IR and UV of compounds 3a-f.

Compound	m.p. (^{0}C)	Yield (%)	R_f value (eluting solvents)	IR ν_{max} in cm^{-1}				λ_{max} (nm) (ε) $\pi\rightarrow\pi^*$
				N-H	C=O non-conj.	C=O arom, C-N	C=C (arom. & bar. acid moieties)	
3a	246-248	28	0.68, ($CHCl_3$:Pet ether, 3.5:1.5)	3400	1695-1670	1620, 1500	1405, 1345, 1260,1110, 1030, 860	282 (1726)
3b	266-269	20	0.74, (neat $CHCl_3$)	3400	1700-1650	1610, 1555	1400, 1335, 1205, 1122, 1080, 1040	293 (10512)
3c	241-243	18	0.80 ($CHCl_3$:Pet ether, 4:1)	3450	1670	1500	1425, 1420, 1300,1045, 945, 690	284 (724)
3d	232-234	16	0.66 ($CHCl_3$:Pet ether, 9:1)	3350	1700	1610, 1550	1445, 1250, 1180,1130, 945, 660	297 (17406)
3e	281-282	24	0.73 ($CHCl_3$: CH_3OH, 8:2)	3425	1680	1630, 1530	1425, 1400, 1300,1050, 950, 1180	284 (1942)s
3f	264-266	23	0.67 ($CHCl_3$: CH_3OH, 9:1)	3450	1675	1630, 1560	1400, 1300, 1225,1130, 1040, 925	402 (4455)
3g	257-259	16	0.64 ($CHCl_3$:Pet ether, 4.7:3)	3450	1675-1695	1540	1400, 1340, 1120, 1015, 820, 760	293 (10512)

The N-H protons at positions 1 and 3 in the compounds 3a-g were strongly deshielded (δ 13.40-7.93) and appeared as singlet in their ^{1}H NMR spectra (Table-3). The N-H protons at position 3 in these compounds were found comparatively more deshielded than protons at position 1. In some compounds (3b, 3d, 3f & 3g), more deshielding of the N-H protons were observed due to presence of thiocarbonyl group. This may be attributed to the greater polarizability of sulfur in comparison to oxygen.

Table 3. ^{1}H NMR spectral data of the compounds 3a-g. [(δ) in ppm].



3a-g

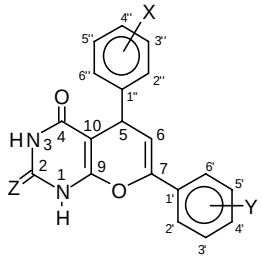
Compound	3-H	1-H	Aromatic	6-H	5-H	X	Y
3a	8.45 (s, 1H, NH)	7.93 (s, 1H,NH)	7.45 (bs, 2H, H-2', H-6') 7.20-7.30 (m, 4H, H-2", H-3", H-5", H-6") 7.13 (bs, 2H, H-3', H-5')	5.70 (bs, 1H)	4.55 (bs, 1H)	2.33 (s,3H) (Ar-CH$_3$)	2.40 (s, 3H) (Ar-CH$_3$)
3b	9.35 (s, 1H, NH)	9.05 (s, 1H, NH)	7.45 (bs, 2H, H-2', H-6') 7.20-7.30 (m, 4H, H-2", H-3", H-5", H-6") 7.14 (bs, 2H, H-3', H-5')	5.70 (bs, 1H)	4.55 (bs, 1H)	2.33 (s,3H) (Ar-CH$_3$)	2.37 (s, 3H) (Ar-CH$_3$)
3c	11.85 (s, 1H, NH)	10.92 (s, 1H, NH)	7.60 (bs, 2H, H-2', H-6') 7.10-7.20 (m, 4H, H-2", H-3", H-5", H-6") 7.00 (bs, 2H, H-3', H-5')	5.85 (bs, 1H)	4.35 (bs, 1H)	2.25 (s,3H) (Ar-CH$_3$)	3.80 (s, 3H) (Ar-OCH$_3$
3d	9.47 (s, 1H, NH)	9.05 (s, 1H, NH)	7.50 (bs, 2H, H-2', H-6') 7.15-7.30 (m, 4H, H-2", H-3", H-5", H-6") 6.90 (bs, 2H, H-3', H-5')	5.60 (bs, 1H)	4.55 (bs, 1H)	2.33 (s, 3H) (Ar-CH$_3$)	3.85 (s, 3H) (Ar-OCH$_3$
3e	10.95 (s, 1H, NH)	10.07 (s, 1H, NH)	7.70 (bs, 2H, H-2', H-6') 7.10-7.20 (m, 4H, H-2", H-3", H-5", H-6") 7.50 (bs, 2H, H-3', H-5')	6.05 (bs, 1H)	4.40 (bs, 1H)	2.25 (s, 3H) (Ar-CH$_3$)	---
3f	11.51 (s, 1H, NH)	11.33 (s, 1H, NH)	7.50 (bs, 2H, H-2', H-6') 7.15-7.25 (m, 4H, H-2", H-3", H-5", H-6") 7.10 (bs, 2H, H-3', H-5')	5.70 (bs, 1H)	4.45 (bs, 1H)	2.30 (s, 3H) (Ar-CH$_3$)	---
3g	13.40 (s, 1H, NH)	12.35 (s, 1H, NH)	7.50 (bs, 2H, H-2', H-6') 7.15-7.25 (m, 4H, H-2", H-3", H-5", H-6") 7.10 (bs, 2H, H-3', H-5')	6.10 (bs, 1H)	4.45 (bs, 1H)	3.37 (s,3H) (Ar-OCH$_3$)	---

The proton at position 6 in **3a-g** appeared as a broad singlet due to the vicinal coupling with the proton at position 5. The chemical shifts were observed at δ 6.10-5.60. The 5-H in these compounds gave signals at δ 4.55-4.35 as broad singlet due to the coupling received from the proton at position 5.

The chemical shifts for the aromatic protons in **3a-g** were found in good agreement with the literature values.[15,16]

The structures of the compounds **3a-g** were further confirmed by their ^{13}C NMR spectra (Table-4). The chemical shifts of carbonyl carbon at 4-C were found to be deshielded in the range of δ 163.48-160.07. The chemical shifts of 9-C were also deshielded (δ 154.51-152.91). This value is comparable with the ^{13}C NMR chemical shifts of cyclohexyl methyl ketone.[17]

Table 4. ^{13}C NMR spectral data of the compounds 3a-g. [(δ) in ppm]



3a-g

Compound	4-C	9-C	7-C	2-C	Aromatic carbons	6-C	10-C	5-C	X	Y
3a	160.23	153.32	147.54	144.52	129.30-124.40	104.50	93.50	35.15	21.30 (Ar-$\underline{C}H_3$)	21.10 (Ar-$\underline{C}H_3$)
3b	160.32	152.91	146.64	172.87	142.91-122.42	103.40	94.00	35.07	21.29 (Ar-$\underline{C}H_3$)	21.09 (Ar-$\underline{C}H_3$)
3c	163.49	154.51	149.89	145.00	160.07-114.20	102.71	87.88	34.61	20.80 (Ar-$\underline{C}H_3$)	55.46 (Ar-O$\underline{C}H_3$)
3d	161.23	154.21	148.42	173.32	161.23-113.32	103.30	91.52	35.21	20.71 (Ar-$\underline{C}H_3$)	55.48 (Ar-O$\underline{C}H_3$)
3e	163.48	154.43	149.87	141.53	129.16-126.10	105.57	87.50	34.70	20.84 (Ar-$\underline{C}H_3$)	---
3f	161.11	153.75	144.00	173.89	140.89-126.13	105.08	92.81	34.62	20.81 (Ar-$\underline{C}H_3$)	---
3g	162.23	153.20	146.32	172.52	160.20-114.32	105.07	93.71	35.52	55.45 (Ar-O$\underline{C}H_3$)	---

In the compounds **3a**, **3c** & **3e**, the chemical shifts of carbonyl carbons at 2-C were found to be at δ 141.53-145.00 and are relatively less deshielded due to the resonance of amide functional group. In the compounds **3b**, **3d**, **3f** & **3g**, the chemical shifts of thioxo carbon at 3-C were found to be at δ 172.52-173.89. This explains that the replacement of a carbonyl group by a thiocarbonyl group results in a downfield shift.[19,20]

The chemical shift values for 7-C and 6-C in these compounds were observed at δ 149.89-144.00 and δ 105.57-102.71 respectively. The 10-C of the compounds showed chemical shift values at δ 94.00-87.50 which were comparable to the earlier report[14] of the ^{13}C NMR spectral data of the monosubstituted barbiturates at 10-C. The chemical shift values for 5-C in these compounds were observed at δ 35.52-34.61.

The ^{13}C NMR chemical shifts for the carbons of aromatic rings were assigned on the basis of a correlation chart available in the literature.[18]

The high resolution mass spectra of the compounds **3a-g** showed peaks for their respective molecular ions (M^+) at m/z 346.20, 362.20, 362.20, 378.15, 366.11, 382.09 and 440.20 respectively. The isotopic pattern for Cl atom (^{35}Cl/^{37}Cl, 3:1) was observed in the molecular mass of **3e** and **3f**. In **3e** the peak for M^+ was 366.11 (17%) and that for M^++2 was 368.12 (6%). In **3f** the peak for M^+ was 440.20 (11%) and that for M^++2 was 442.22 (4%).

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