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A One Pot 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)

M. Mahbubur Rahman[1], S. Mosaddeq Ahmed[2], S. M. A. Hakim Siddiki[3], Md. Ershad Halim[1], Kawsari Akhter[1], M. Giasuddin Ahmed[1] and U. K. R. Romman[1]*

[1]*Department of Chemistry, Dhaka University, Dhaka-1000, Bangladesh*

[2]*Department of Natural Science, American International University-Bangladesh (AIUB), Banani, Dhaka-1213, Bangladesh*.

[3]*Graduate School of Material Science, University of Hyogo, 678-1297, Japan*

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Abstract

A number 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) (**3a-f**) have been synthesized in one-step by cyclocondensation of barbituric acid or thiobarbituric acid (**1**) with arylideneacetophenones (**2a-c**), in glacial acetic acid in the presence of phosphorous pentoxide. The structures of the compounds **3a-f** have been determined by UV, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.

Keywords: arylideneacetophenone, barbituric acid, thiobarbituric acid, cyclocondensation.

I. Introduction

Synthesis of pyranopyrimidines has been an interesting work because of the pharmacological activities[1-4] associated with this system. A variety of routes[5-8] for the synthesis of these compounds have been reported, but the majority of them involve a number of steps and the yields are relatively poor. This initiated 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.

Having this background, in continuation of the reported works[10,11] on the synthesis of 5, 7-diaryl-1, 5-dihydro-pyrano[2,3-*d*]pyrimidin-2, 4-diones, we report herein syntheses of 5-(4-chloro-phenyl)-7-phenyl-1, 5-dihydro-pyrano[2, 3-*d*]pyrimidine-2, 4-dione **3a**, 5-(4-chloro-phenyl)-7-*p*-tolyl-1, 5-dihydro-pyrano[2, 3-*d*]pyrimidine-2,4-dione **3b**, 5-(4-chloro-phenyl)-7-phenyl-2-thioxo-1, 2, 3, 5-tetrahydro-pyrano[2, 3-*d*]pyrimidine-4-one **3c**, 5-(4-chloro-phenyl)-2-thioxo-7-*p*-tolyl-1, 2, 3, 5-tetrahydro-pyrano[2, 3-*d*]pyrimidine-4-one **3d**, 5-(4-chloro-phenyl)-7-(4-nitro-phenyl)-1, 5-dihydro-pyrano[2, 3-*d*]pyrimidine-2, 4-dione **3e** and 5-(4-chloro-phenyl)-7-(4-nitro-phenyl)-2-thioxo-1, 2, 3, 5-tetrahydro-pyrano[2, 3-*d*]pyrimidin-4-one **3f** by selecting a number of arylideneacetophenones (**2a-c**) 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.

The Compounds **3a-f** have been characterized by different spectroscopic methods and elemental analyses. The formation of compounds **3a-f** 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.

*Author for Correspondence, *e-mail*: uromman@yahoo.com

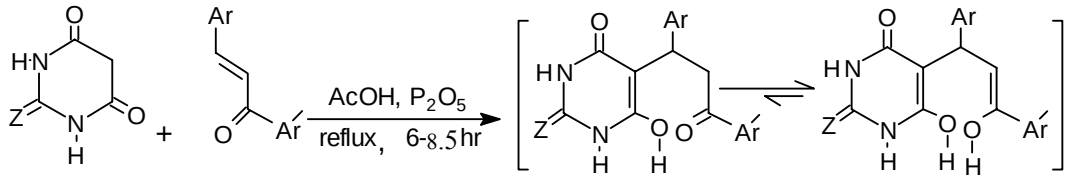
II. Experimental

The UV spectra were run in methanol using SHIMADZU-UV-160A ultraviolet spectrophotometer with a scanning range of 800-200 nm using methanol as solvent. The IR spectra were recorded as KBr pellet using SHIMADZU FT-IR 8400S infra-red spectrophotometer in the range of 4000-400 cm^{-1}. The ^{1}H- and ^{13}C- NMR spectra were recorded on 600 MHz NMR spectrometer. The solvent used was d_6- DMSO and TMS is being used as a reference. All the compounds gave expected C, H and N analyses.

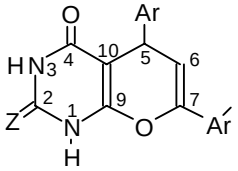
3-(4-chloro-phenyl)-1-phenyl propenone **2a**, 3-(4-chloro-phenyl)-1-*p*-tolyl-propenone **2b** and 3-(4-chloro-phenyl)-1-(4-nitro-phenyl)-propenone **2c** were prepared from the reactions of corresponding substituted aldehydes and substituted acetophenones by following primarily literature method[13] 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 (10 mL) and P_2O_5 (2 g) 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 6-8.5 hours and the course of the reaction was followed by TLC on silica gel plates (eluting solvent; EtOAc: $CHCl_3$ =3:2). The mixture was allowed to cool and treated with crushed ice. The solid, thus obtained, was filtered off, washed with cold water, dried and purified by recrystallization from rectified spirit.

Scheme-1



Product	Z	Ar	Ar´
3a	O	4-ClC$_6$H$_4$	C$_6$H$_5$
3b	O	4-ClC$_6$H$_4$	4-H$_3$CC$_6$H$_4$
3c	S	4-ClC$_6$H$_4$	C$_6$H$_5$
3d	S	4-ClC$_6$H$_4$	4-H$_3$CC$_6$H$_4$
3e	O	4-ClC$_6$H$_4$	4-O$_2$NC$_6$H$_4$
3f	S	4-ClC$_6$H$_4$	4-O$_2$NC$_6$H$_4$

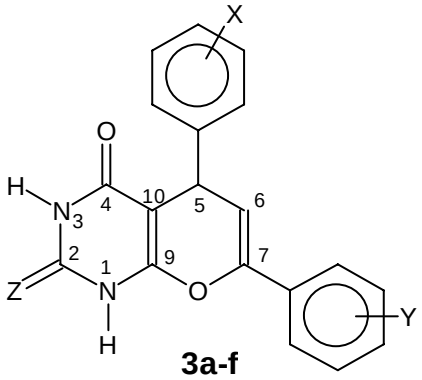


3a-f

(1:1 ratio)

III. Results and Discussion

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



3a-f

Substituent	3a	3b	3c	3d	3e	3f
X	4-Cl	4-Cl	4-Cl	4-Cl	4-Cl	4-Cl
Y	H	4-CH$_3$	H	4-CH$_3$	4-NO$_2$	4-NO$_2$
Z	O	O	S	S	O	S

In their UV spectra of compounds **3a-f** the observed λ_{max} values agree well to the expected values. The absorption bands in the range 312-286 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 312-286 nm.

The IR data of the compounds **3a-f** (Table 2) showed sharp as well as broad bands in the range (ν_{max}) 3476-3100 cm^{-1} indicating the presence of N-H group. The absorption bands

at 1759-1655 cm^{-1} indicate the presence of non-conjugated C=O stretching including the barbituric acid moieties.[14] The bands at 1606-1514 cm^{-1} were assigned to C=C of aromatic rings and C=N of the conjugated form of barbituric acid part. Additional bands were observed at 1451-813 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	8	135	64.05 (64.69)	3.65 (3.71)	7.05 (7.94)	$C_{19}H_{13}N_2O_3Cl$	352.5
3b	8.5	140	64.32 (65.49)	4.39 (4.12)	7.32 (7.64)	$C_{20}H_{15}N_2O_3Cl$	366.5
3c	7	135	63.49 (64.21)	4.35 (4.15)	7.80 (7.85)	$C_{19}H_{13}N_2O_2ClS$	368.5
3d	6.5	138	63.56 (62.74)	4.30 (4.10)	7.56 (7.32)	$C_{20}H_{15}N_2O_2ClS$	382.5
3e	6	140	58.48 (57.37)	3.15 (3.04)	10.15(10.56)	$C_{19}H_{12}N_3O_5Cl$	397.5
3f	6	143	58.75 (58.15)	3.25 (3.15)	10.24(10.30)	$C_{19}H_{12}N_3O_4ClS$	413.5

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}				UV, λ_{max} (nm) (ε)
				N-H	C=O non-conj.	C=O arom, C-N	C=C (arom. & bar. acid moieties)	$\pi\rightarrow\pi^*$, $n\rightarrow\pi^*$
3a	312-314	58	0.33 ($EtOAc:CHCl_3$=3:2)	3230	1759, 1718	1603, 1514	1417, 1240, 1028, 819	286 (3780)
3b	141-142	77	0.71 ($EtOAc:CHCl_3$= 3:2)	3474	1655	1599	1332, 1012, 813	312 (25994)
3c	310-312	70	0.81 ($EtOAc:CH_3OH$=3:2)	2857	1680	1606, 1563	1451, 1220, 1110, 1050, 827	286 (3925)
3d	281-284	85	0.41 ($EtOAc:CHCl_3$ =3:2)	3046	1680	1600, 1558	1450, 1120, 815	286 (5078)
3e	298-300	76	0.32 ($EtOAc:CHCl_3$ =4:1)	3290	1726, 1683	1607, 1518	1437, 1348, 1286, 1101, 856	301 (2475)
3f	126-128	52	0.58 ($EtOAc:CHCl_3$ = 4:1)	3476	1681	1583	1347, 1138, 854	317 (10453)

The N-H protons at positions 1 and 3 in the compounds **3a-f** were strongly deshielded (δ 12.51-10.95) 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 (**3c**, **3d** & **3f**) 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-f. [(δ) in ppm].

Compound	3-H	1-H	Aromatic	6-H	5-H	X	Y
3a	11.85 (s,1H,NH)	10.95 (s,1H,NH)	8.20-7.20 (m, 9H)	6.05 (bs,1H)	4.40 (bs, 1H)	…..	…..
3b	11.80 (s,1H, NH)	10.98 (s,1H,NH)	8.10-7.20 (m, 8H)	5.90 (bs,1H)	4.40 (bs,1H)	……	2.50-2.25 (m 3H) (Ar-CH_3)
3c	12.40 (s,1H, NH)	12.00 (s,1H,NH)	7.80-7.20 (m, 9H)	6.10 (bs,1H)	4.50 (bs,1H)	……	……
3d	12.40 (s,1H, NH)	12.10 (s,1H,NH)	7.60-7.20 (m, 8H)	5.90 (bs,1H)	4.50 (bs,1H)	……	2.35 (s, 3H) (Ar-CH_3)
3e	11.50 (s,1H, NH)	11.00 (s,1H,NH)	8.30-7.30 (m, 8H)	6.30 (bs,1H)	4.50 (bs,1H)	……	……
3f	12.51 (s,1H, NH)	11.95 (s,1H,NH)	8.30-7.20 (m, 8H)	5.70 (bs,1H)	4.45 (bs,1H)	……..	……

The proton at position 6 in **3a-f** appeared as a broad singlet due to the vicinal coupling with the proton at position 5. The chemical shifts were observed at δ 6.30-5.70. The 5-H in these compounds gave signals at δ 4.50-4.40 as broad singlet due to the coupling received from the proton at position 5.

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

The structures of the compounds **3a-f** 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 188.47-160.96. The chemical shifts of 9-C were also deshielded (δ 163.48-150.60). 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-f. [(δ) in ppm]

Compound	4-C	9-C	7-C	2-C	Aromatic carbons	6-C	10-C	5-C	X	Y
3a	172.08	163.48	154.67	144.47	139.89-126.10	104.02	87.54	35.11	…….	……
3b	188.47	163.30	154.55	145.23	143.74-122.78	102.98	87.08	34.35	……	20.80 (Ar-CH_3)
3c	160.96	153.23	143.93	173.77	133.78-125.96	104.76	92.45	34.85	……	…….
3d	160.99	158.47	146.00	183.01	142.94-123.25	105.75	92.13	34.28	…….	20.80 (Ar-CH_3)
3e	163.21	150.60	147.44	143.52	131.26-123.93	108.22	87.12	34.59	…….	……
3f	163.11	150.75	146.80	173.89	140.89-126.13	105.08	92.81	34.62	……	…..

In the compounds **3a**, **3b** and **3e**, the chemical shifts of carbonyl carbons at 2-C were found to be at δ 145.23-143.52 and are relatively less deshielded due to the resonance of amide functional group. In the compounds **3c**, **3d** and **3f**, the chemical shifts of thioxo carbon at 2-C were found to be at δ 183.01-173.77. 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 154.67-143.93 and δ 108.22-102.98, respectively. The 10-C of the compounds showed chemical shift values at δ 92.81-87.08 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 35.11-34.28.

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 compounds **3a-f** showed peaks for their respective molecular ions (M^+) with sodium in their high resolution mass spectra at m/z 375.7708 (22.50%), 389.6605 (9%), 391.0455

(12%), 405.8605 (11.11%), 420.7580 (6%) and 436.5430 (10%) respectively. The isotopic pattern for Cl atom ($^{35}Cl/^{37}Cl$, 3:1) was observed in the molecular mass of the compounds **3a-f**. The M^{+}+2 with Na were observed at 377.2050 (7.50%), 391.7650 (3%), 393.0450 (4%), 407.0180 (3.7%), 422.3205 (2%) and 438.5033 (3.25%) respectively.

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