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A Study on the Synthesis of 5, 7-Diaryl-1,2,3,4-tetrahydro-2, 4-dioxo-5*H*-pyrano [2,3-*d*]pyrimidines

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Abstract

5,7-Diphenyl-1,2,3,4-tetrahydro-2,4-dioxo-5*H*-pyrano[2,3-*d*]pyrimidine **(4a)** has been synthesized in single-step by the condensation of barbituric acid **(1)** with benzylideneacetophenone **(2a)** in glacial acetic acid in the presence of phosphorous pentoxide. Reaction of barbituric acid **(1)** with arylideneacetophenones **(2b-d)** which gave the corresponding adducts of 5-(1,3-diaryl-1-oxopropyl) pyrimidine (1H, 3H, 5H)-2,4,6-triones **(3a-c)** previously in 50 % aqueous ethanol which on further reflux in gl. acetic acid in the presence of phosphorous pentoxide also gave the corresponding pyranopyrimidines 5,7-diaryl-1,2,3,4-tetrahydro-2,4-dioxo-5*H*-pyrano[2,3-*d*]pyrimidines **(4b-d)**. The structures of the compounds **4a-d** were characterized by their UV, IR, ^{1}H NMR and ^{13}C NMR spectral data.

Introduction

It has been a continuous interest in the synthesis of pyranopyrimidines because of their pharmacological activities associated with this system.[1,2] A large number of reports is available on the reactions of barbituric acid and thiobarbituric acid with carbonyl compounds- aldehydes, ketones and esters.[3-21] But it is observed that very little extent of work has been done on the reactions of barbituric acid and thiobarbituric acid with α,β-unsaturated carbonyl systems.[17,19,22,23]

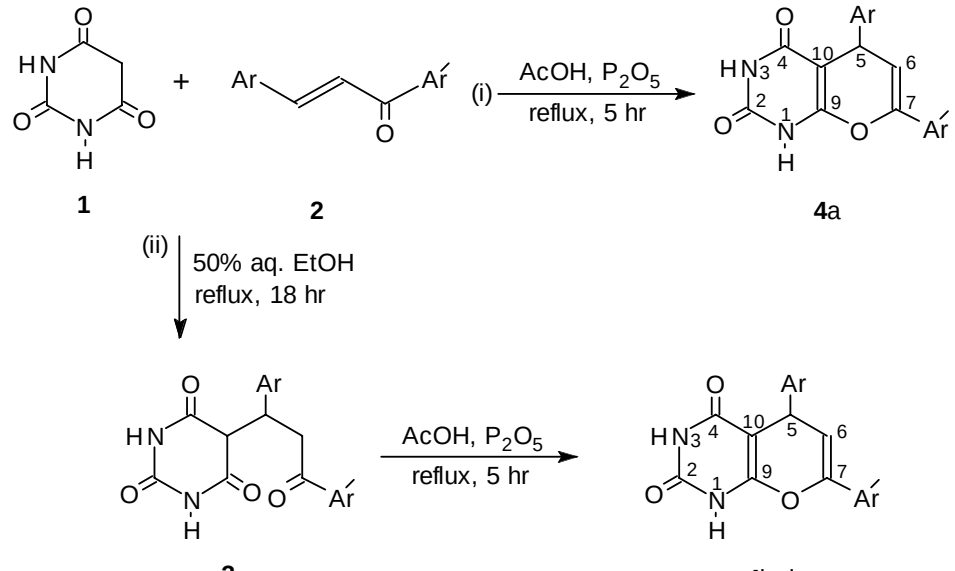
Although various routes for the synthesis of these compounds have been described, the majority of them involve a number of steps and the yields are poor.[23] Therefore, it is felt necessary to develop an efficient method for the synthesis of these compounds relatively in good yields.

With this background, in continuation of our series of works[24-27] on barbituric acid and thiobarbituric acid derivatives in the present paper, we report herein a one-step and three two-steps syntheses of 5,7-diaryl-1,2,3,4-tetrahydro-2,4-dioxo-5*H*-pyrano[2,3-*d*] pyrimidines **(4a-d)** in good yields (Scheme-1). These compounds were synthesized by selecting a number of arylideneacetophenones[28-30] **(2a-d)** as the α,β-unsaturated carbonyl system having different substituents on the aromatic rings for reaction with barbituric acid **(1)** as the active methylene component involving Michael type addition. The compounds **4a-d** do not seem to be available in the literature. The compounds were characterized with the help of their spectral properties.

Materials and Methods

The UV spectra were run in methanol using SHIMADZU, UV-160A ultraviolet spectrophotometer. The IR spectra were recorded as KBr pellet using SHIMADZU IR-470

Scheme-1



1 **2** **4**a **3** **4**b-d

	Ar	Ar′
2a	C_6H_5	C_6H_5
b	4-ClC_6H_4	4-$CH_3OC_6H_4$
c	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$
d	C_6H_5	4-$O_2NC_6H_4$

1 + **2**b = **3**a
1 + **2**c = **3**b
1 + **2**d = **3**c

	Ar	Ar′
4a	C_6H_5	C_6H_5
b	4-ClC_6H_4	4-$CH_3OC_6H_4$
c	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$
d	C_6H_5	4-$O_2NC_6H_4$

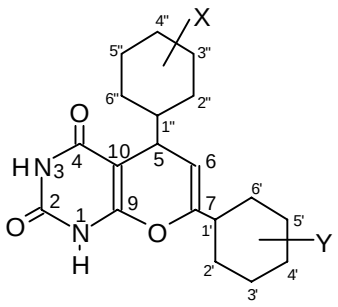
infra-red spectrophotometer in the range of 4000-400 cm^{-1}. The ^1H NMR spectra were recorded on a Bruker 400 MHz NMR spectrophotometer. The solvents used were deuterated DMSO for compounds **1a, 1b** and **1d** and $CDCl_3$ for compound **1c**. The reactions described in the present paper were carried out following a general procedure.[23]

General Procedure

(i) A mixture of benzylideneacetophenone (0.005 mol) and barbituric acid (0.005 mol) were dissolved in acetic acid (15ml) and P_2O_5 (2g) in a round-bottomed flask equipped with a refluxing condenser and a drying tube placed in a paraffin oil bath on a magnetic stirrer. The reaction mixture was refluxed at 120^O C for 5 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 benzene. (ii) A mixture of arylideneacetophenone (0.005 mol) and barbituric acid (0.005 mol) were dissolved in a solution of rectified spirit (25 ml) and water (25 ml) in a round-bottomed flask equipped with a refluxing condenser placed in a paraffin oil bath on a magnetic stirrer. The reaction mixture was refluxed for 18 hours and the course of the reaction was followed by TLC on silica gel plates (eluting solvent; EtOAC : MeOH; 10:1). The mixture was allowed to cool and the solid separated out was dried in air and recrystallized from rectified spirit.

Results and Discussion

Compound **4a** was synthesized directly from **1** and **2a,** and compound **4b-d** were synthesized by carrying out reactions of adducts



4a-d

Substituent	4a	4b	4c	4d
X	H	*4*-Cl	*4*-CH_3	H
Y	H	*4*-OCH_3	*4*-OCH_3	*4*-NO_2

5-(1, 3-diaryl-1-oxopropyl) pyrimidine (1H, 3H, 5H)-2,4,6-triones **(3a-c)** in presence of acetic acid and P_2O_5 under reflux following a general experimental procedure which was based on a known method.[23] The time and temperature of the reactions were modified as required. The assignment of the structures of the compounds **4a-d** was made on the basis of their UV, IR, ^{1}H NMR, ^{13}C NMR spectral data.

The observed λ_{max} values of compounds **4a-d** agree well to the expected values in their UV spectra. The absorption bands in the range 274-251 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 com pounds due to C=O were probably masked by the $\pi\rightarrow\pi^*$ absorption range of 274-251 nm. The absorption bands at 219-213 nm may be assigned to the $\pi\rightarrow\pi^*$ in the aromatic rings and barbituric acid residues in these compounds. As reported,[2] the absorptions due to the $n\rightarrow\pi^*$ transitions in the heterocyclic rings in these structures were hidden within the range of $\pi\rightarrow\pi^*$ absorption (219-213 nm).

The IR data of the compounds **4a-d** (Table II) showed sharp as well as broad bands in the range (ν_{max}) 3155-3100 cm^{-1} indicating the presence of N-H group. The absorption bands at 1710-1680 cm^{-1} indicate the presence of non-conjugated C=O stretching including the barbituric acid moieties.[2,19]

Table II. Physical constants, IR and UV of compounds 4a-d

Compound	m.p. (^{O}C)	Yield %	IR, ν_{max} in cm^{-1}	UV, λ_{max} (nm)
4a	290-292	80	3100, 1700, 1675, 1620, 1590, 1500, 1430, 1350, 1155, 1110,1040, 820, 750, 700	251, 218
4b	210-212	81	3155, 3100, 1700, 1680, 1595, 1500, 1410, 1300, 1250, 1200, 1170, 1100, 1025, 830, 765,750	260, 219
4c	294-295	79	3150, 2070, 1700, 1680, 1570, 1505, 1450, 1360, 1310, 1160, 1100, 1030, 820, 760	258, 219
4d	280-282	80	3150, 1710, 1680, 1620, 1510, 1440, 1400, 1340, 1280, 1260, 1200, 1180, 1100, 1040, 970, 850, 740, 700	274, 213

[23]molar ratio (1:1, 0.003 mol), refluxing time (45-60min), CH_3COOH (10 ml), P_2O_5 (1g) and yield % (77-92)

The bands at 1620-1505 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 1100-1450 cm^{-1} due to these structural units.[19,22]

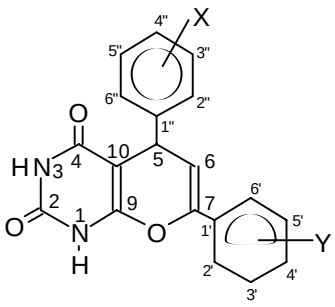
The N-H protons in the compounds **4a-d** were strongly deshielded (δ 11.02-10.96) and appeared as multiplet in their ^{1}H NMR spectra (Table III). The proton at position 6 in 4a-d appeared as a doublet due to the vicinal coupling with the proton at position 5. The chemical shifts were observed at δ 6.28-5.74 with J values 3.5-4.0 Hz. The 5-H in these compounds gave signals at δ 4.49-4.39 as doublet due to the coupling of 5-H by 6-H with J values 3.5-4.0 Hz.

The chemical shifts for the aromatic protons in **4a-d** were found in good agreement with the literature values.[31]

The structures of the compounds **4a-d** were further confirmed by their ^{13}C NMR spectra

Table III. ^{1}H NMR spectral data of the compounds 4a-d. [(δ) in ppm and (J) in Hz]

Compound	1-H and 3-H	Aromatic protons	6-H	5-H	X	Y
4a	11.00 (m, 2H, N<u>H</u>)	7.64-7.26 (m, 10H)	5.97 (d, $J_{6,5}$=4.0, 1H)	4.43 (d, $J_{5,6}$6=4.0, 1H)	---	---
4b	10.96 (m, 2H, N<u>H</u>)	7.55 (d, J=7.89, 2H, H-2′ and 6′) 7.27 (d, J=8.92, 4H, H-2′′, 3′′, 5′′ and 6′′) 6.93 (d, J=7.91, 2H, H-3′ and 5′)	5.74 (d, $J_{6,5}$=3.8, 1H)	4.39 (d, $J_{5,6}$=3.9, 1H)	---	3.37 (s, 3H) (4-OC<u>H</u>$_3$)
4c	11.02 (m, 2H, N<u>H</u>)	7.94 (d, J=8.50, 2H, H-2′ and 6′) 7.52-7.04 (m, 4H, H-2′′, 3′′, 5′′ and 6′′) 6.95 (d, J=8.75, H-3′ and 5′)	5.89 (d, $J_{6,5}$=3.5, 1H)	4.49 (d, $J_{5,6}$=3.6, 1H)	2.35 (s, 3H) (4-C<u>H</u>$_3$)	3.73 (s, 3H) (4-OC<u>H</u>$_3$)
4d	10.99 (m, 2H, N<u>H</u>)	8.22 (d, J=8.01, 2H, H-3′ and 5′) 7.88 (d, J=8.01, 2H, H-2′ and 6′) 7.27-7.19 (m, 5H, H-2′′, 3′′, 5′′ and 6′′)	6.28 (d, $J_{6,5}$=3.7, 1H)	4.47 (d, $J_{5,6}$=3.6, 1H)	---	---

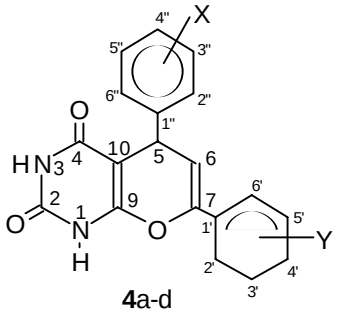


4a-d

(Table IV). The chemical shifts of carbonyl carbon at 4-C were found to be deshielded in the range of δ 164.40-163.65. The chemical shifts of 9-C were also deshielded (δ 160. 80-154.60). This value is comparable with the ^{13}C NMR chemical shifts of cyclohexyl methyl ketone.[32] In these compounds the carbonyl carbons at positions 2 and 4 were

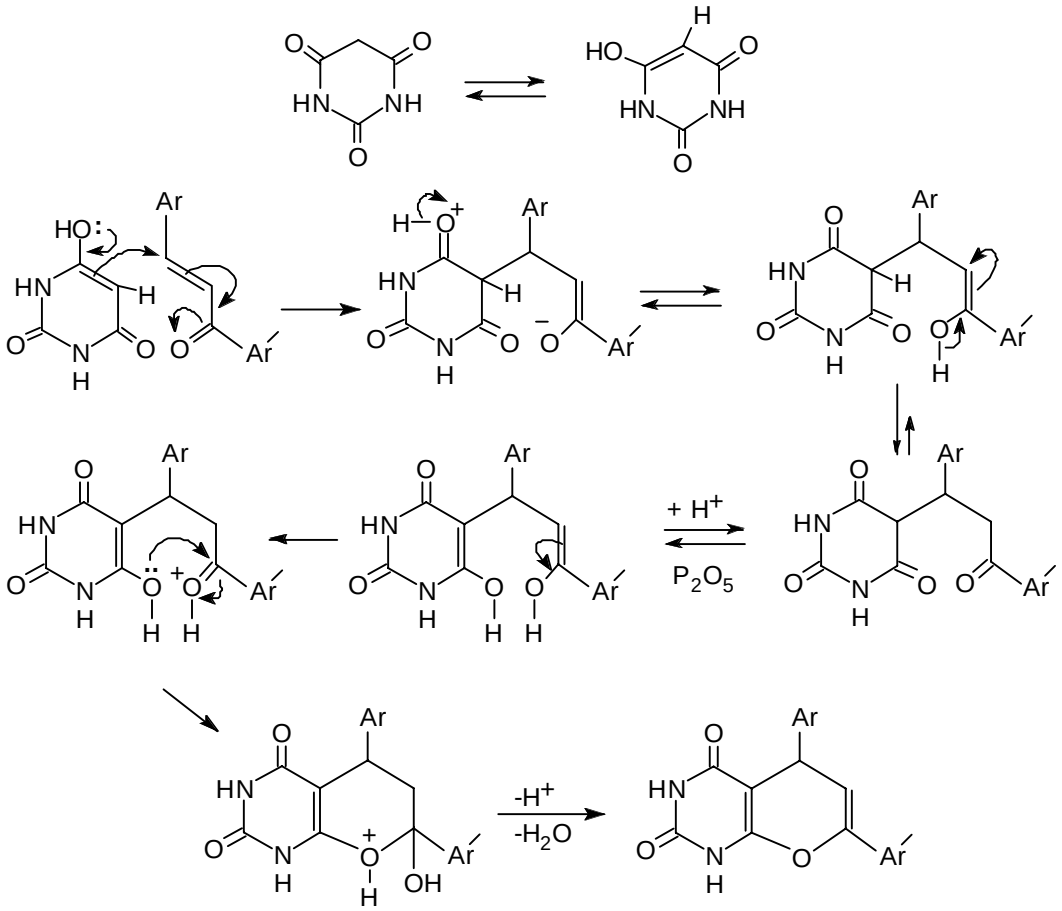
Table IV. ^{13}C NMR spectral data of the compounds 4a-d. [(δ) in ppm]

Compound	4-C	9-C	7-C	2-C	Aromatic	6-C	10-C	5-C	X	Y
4a	163.98	155.77	150.85	145.46	144.89-124.46	104.90	87.74	35.23	---	---
4b	164.23	160.32	154.93	150.09	163.74 (C-4′) 124.02 (C-3′) 114.33 (C-5′) 145.33-126.09 (rest of the carbons)	102.18	87.74	34.66	---	55.55 (O<u>C</u>H$_3$)
4c	164.40	160.80	153.90	151.50	161.20 (C-4′) 134.70 (C-1′′, 4′′) 129.10 (C-2′′, 3′′, 5′′& 6′′) 127.20 (C-1′, 2′ & 6′) 114.00 (C-3′ & 5′)	101.50	87.50	33.00	20.90 (<u>C</u>H$_3$)	56.00 (O<u>C</u>H$_3$)
4d	163.65	154.60	150.02	144.05	147.68 (C-4′) 143.71 (C-1′) 137.74 (C-1′′) 130.17 (C-2′′) 129.40 (C-6′′) 128.86 (C-3′′) 128.67 (C-5′′) 128.07 (C-2′) 127.14 (C-6′) 125.13 (C-4′′) 124.20 (C-3′ & 5′)	109.09	87.69	35.37	---	---



4a-d

Scheme-2



found to be deshielded (δ 164.40-144.05) and showed different chemical shifts. The non-equivalence of these carbons are caused by the different environment of two carbonyl groups at positions 2 and 4.

The chemical shift values for 7-C and 6-C in these compounds were observed at δ 154.93-150.02 and δ 109.09-101.50 respectively. The 10-C of the compounds showed chemical shift values at δ 87.74-87.50 which were comparable to the earlier report[2] 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 35.37-33.00.

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.[33]

A plausible mechanism for the formation of the compounds **4a-g** is outlined (Scheme-2):

Acknowledgement

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