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A ONE-POT SYNTHESIS OF 7,11-DIARYL-2,4-DIAZASPIRO[5,5]UNDECANE - 3-OXO (OR THIOXO)-1,5,9-TRIONES

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Abstract

Spiro compounds 7,11-diaryl-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraones **3a-d** were prepared by carrying out reactions between diarylideneacetones, $(ArCH=CH)_2C=O$, **2a-d** [Ar= *2*-$CH_3C_6H_4$, *4*-$CH_3C_6H_4$, *4*-$(CH_3)_2NC_6H_4$ and *4*-HOC_6H_4 respectively] and barbituric acid (**1a**) under refluxing condition in aqueous ethanol medium without using any catalyst. Under similar conditions the corresponding 7,11-diaryl-3-thioxo-2,4-diazaspiro[5,5]undecane-1,5,9-triones **3e-g** were synthesized from the reactions of diarylideneacetones **2a, 2d** and **2e** [Ar= *4*-ClC_6H_4] with 2-thiobarbituric acid (**1b**). The structures of the spiro compounds were established with the help of their UV, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and elemental analyses.

Introduction

A voluminous literature[1,2] has grown up in the field of synthesis and pharmaceutical activity of barbiturates and thiobarbiturates over the period of more than a century. Due to presence of an active methylene group at the 5-position reports on the 5-substituted barbituric acid and thiobarbituric acid derivatives are much more numerous than those on other barbiturates. A large number of reports[3-15] are available on the reactions of barbituric acid and thiobarbituric acid with carbonyl compounds- aldehydes, ketones and esters; and on the pharmaceutical activity of the products obtained. In almost all these cases active methylene group at the 5-position was involved in causing the reaction. An updated literature survey shows that little work [3,6,7] has been done on reactions of α,β-unsaturated carbonyl systems with **1a** and **1b.**

With this background, we focused our work on the reaction of diarylideneacetones with **1a** and **1b** with a view to synthesizing potential medicinal compounds. In continuation to our previous works[16-20], we selected a number of 1,5-diaryl-1,4-pentadien-3-ones[21] (**2a-e**) for reaction with barbituric acid (**1a**) and thiobarbituric acid (**1b**) (Scheme-1). We would like to report herein the synthesis of hitherto unknown compounds **3a-g** and their characterization with the help of their UV, IR, NMR (^{1}H and ^{13}C), MS and elemental analyses.

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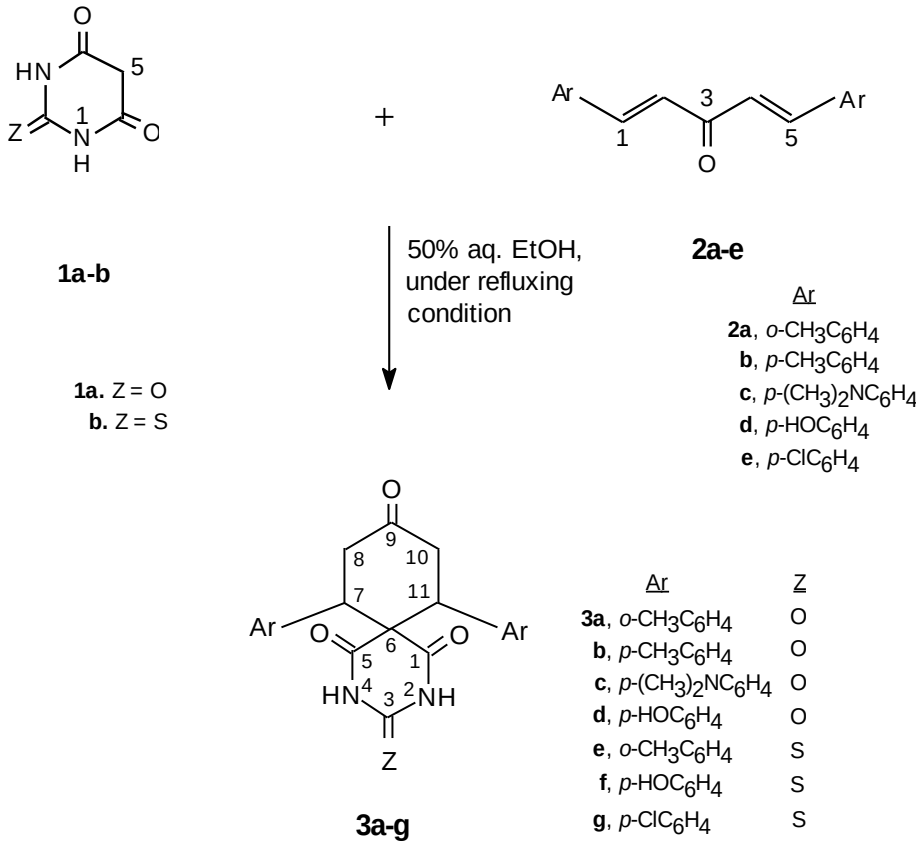
Scheme-1



Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. High resolution mass spectra were recorded at the Graduate School of Sciences, Kyushu University, Fukuoka, Japan. Melting points were determined in open ended capillary tubes and were uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded in d_6 DMSO. IR spectra were run as KBr pellets on a SHIMADZU IR-470 spectrophotometer. UV spectra were run by using methanol SHIMADZU UV-160A spectrophotometer.

1,5-Diaryl-1,4-pentadien-3-ones **2a-e** were prepared primarily by following the literature method[22] with modifications wherever necessary[21]. The reactions described in the present paper were carried out following a general procedure.

*General Procedure***.** A mixture of 1,5-diaryl-1,4-pentadien-3-ones (0.005 mol) and barbituric acid/2-thiobarbituric acid (0.005 mol) were dissolved in rectified spirit (25 ml)

and water (25 ml) in a round-bottomed flask equipped with a magnetic stirrer and a refluxing condenser. The reaction mixture was refluxed for 18-20 h and the course of the reaction was followed by tlc on silica gel plates (eluting solvent; $CHCl_3$:EtOAc, 5:1 if not otherwise mentioned). The mixture was allowed to cool and a solid separated out which was filtered, dried and recrystallized from rectified spirit.

7,11-Bis-(2-methylphenyl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone, 3a: White solid, m. p. 246-248^{0}C, R_f in tlc 0.62, Yield 57%. UV: λ_{max} (nm) (ε) 267 (843), 216 (7418). IR: ν_{max} (cm^{-1}) 3220, 1750, 1700, 1670, 1560, 1520. MS: m/z 390.2 (M^+) (5), 392.2 (M^++2) (100), 263.2 (17), 231.2 (47), 145.1(40), 136.1 (28), 91.0 (12). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.58; H, 5.69; N, 7.18 %.

7,11-Bis-(4-methylphenyl)2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone, 3b: White solid, m. p. 261-262^{0}C, R_f in tlc 0.60 (Pet-ether 60-80: $CHCl_3$, 1:4), Yield 40%. UV: λ_{max} (nm) (ε) 224 (12123). IR: ν_{max} (cm^{-1}) 3200, 1750, 1710, 1670, 1605. MS: m/z 390.11(M^+) (1), 391.11 (M^++1) (2), 392.1 (M^++2) (3), 303.1 (15), 251.1 (49), 154.1(100), 136.1 (90), 89.0 (29). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.68; H, 5.59; N, 7.16 %.

7,11-Bis-(4-dimethylamino-phenyl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone, 3c: Red solid, m. p. 227-228^{0}C, R_f in tlc 0.63, Yield 35%. UV: λ_{max} (nm) (ε) 266 (12895), 213 (7737). IR: ν_{max} (cm^{-1}) 3210, 1750, 1710, 1675, 1610, 1515. MS: m/z 448.3 (M^+) (100), 447.3 (57), 328.2 (11), 258.2 (47), 174.1 (74), 154.1(59), 107.0 (14), 57.1 (5). Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49. Found: C, 66.44; H, 6.31; N, 12.22 %.

7,11-Bis-(4-hydroxyphenyl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraone, 3d: Brown solid, m. p. 272-273^{0}C, R_f in tlc 0.46 (Pet-ether 60-80: EtOAc, 1:2), Yield 56%. UV: λ_{max} (nm) (ε) 277 (6073), 231 (27386). IR: ν_{max} (cm^{-1}) 3400, 3200, 1740, 1700, 1680, 1600, 1500. MS: m/z 394.19 (M^+) (4), 395.21 (11), 307.2 (25), 289.2 (13), 233.2 (3), 154.1 (100), 136.1 (65), 89.0 (12). Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.81; H, 4.58; N, 7.09 %.

7,11-Bis-(2-methylphenyl)-3-thioxo-2,4-diaza-spiro[5.5]undecane-1,5,9-trione, 3e: Yellow solid, m. p. 234-235^{0}C, R_f in tlc 0.66, Yield 54%. UV: λ_{max} (nm) (ε) 293 (6228), 218 (4268). IR: ν_{max} (cm^{-1}) 3175, 1700, 1675, 1625, 1535. MS: m/z 406.25 (M^+) (9), 407.3 (M^++1) (100), 289.2 (28), 247.2 (56), 154.1 (60), 136.1 (46), 91.1 (12). Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.57; H, 5.50; N, 6.92 %.

7,11-Bis-(4-hydroxyphenyl)-3-thioxo-2,4-diaza-spiro[5.5]undecane-1,5,9-trione, 3f: Brown solid, m. p. 241-242^{0}C, R_f in tlc 0.58 (Pet-ether 60-80: EtOAc, 1:2), Yield 48%. UV: λ_{max} (nm) (ε) 286 (29524), 232 (26296). IR: ν_{max} (cm^{-1}) 3390, 3200, 1720, 1700, 1670, 1600, 1500. MS: m/z 410.19 (M^+) (8), 411.2 (M^++1) (23) 307.2 (38), 289.2 (20),

154.1 (100), 136.1 (60), 89.0 (10). Anal. Calcd for $C_{21}H_{18}N_2O_5S$: C, 61.45; H, 4.42; N, 6.83. Found: C, 60.88; H, 4.45; N, 6.85 %.

7, 11-Bis-(4-chlorophenyl)-3-thioxo-2, 4-diaza-spiro[5.5]undecane-1, 5, 9-trione, 3g: White solid, m. p. 245-246^{0}C, R_f in tlc 0.65, Yield 51%. UV: λ_{max} (nm) (ε) 284 (37278), 224 (29404). IR: ν_{max} (cm^{-1}) 3400, 1720, 1680, 1520. MS: m/z 447.14 (M^+) (19), 449.12 (M^++2) (7), 437.35 (11), 393.3 (10), 307.2 (28), 289.2 (18), 154.1 (100), 136.1 (61), 89.0 (12). Anal. Calcd for $C_{21}H_{16}Cl_2N_2O_3S$: C, 56.38; H, 3.60; N, 6.26. Found: C, 55.97; H, 3.64; N, 6.01 %.

Results and Discussion

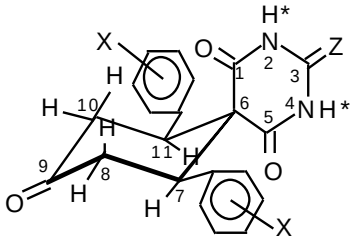
Compounds **3a-g** showed all expected λ_{max} values in their UV spectra (see Experimental section) in the range of 213-277 and 284-293 nm due to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions as reported[2,7,16] previously. The IR data (see Experimental) of these compounds showed sharp and broad bands in the range (ν_{max}) 3175-3400 cm^{-1} for the N-H groups. The compounds **3d** and **3f** in addition gave broad bands in the same range due to O-H stretching. All other typical absorptions for **3a-g** correspond well to expected ν_{max} values.[2,7,16]

In their ^{1}H NMR spectra (Table 1) the N-H protons of the compound **3a-d** at position 2 and 4 are strongly deshielded (δ11.00-11.84) since they are flanked by two C=O groups. The non-equivalence of these protons are caused by the anisotrophy of the C-1 and C-5 carbonyl groups owing to the geometry of spiro structures as reported[2,16] earlier. The N-H protons at position 2 and 4 in the compounds **3e-g** obtained from the reaction with **1b** are more deshielded (δ12.03-12.83) than those in the compounds **3a-d** produced in the reactions with **1a**. This may be attributed to the greater polarizability of sulfur compounds in comparison to oxygen. This causes more deshielding of the N-H protons in the sulfur compounds **3e-g**.

Although axial protons are shielded than equatorial protons the axial protons at positions 7, 8, 10 and 11 are considerably deshielded and appeared at δ 3.19-4.61. The equatorial protons at positions 8 and 10 resonated at higher field (δ2.35-2.53) than the axial protons of these positions. This may be explained by the proximity of the axial protons at 7, 8, 10 and 11 positions to the aromatic rings present at positions 7 and 11. The anisotropic effect of C=O on H_{eq} at C-8 and C-10 is also responsible for diamagnetic shift of these protons.

The structures of the compounds **3a-g** were further confirmed by their ^{13}C NMR spectra (Table 2). The chemical shift values are in good agreement with those of reported earlier[16] for similar compounds. In the compounds **3a-d**, chemical shifts of carbonyl carbons at C-3 were found to be at δ 148.75-150.73 and are relatively less deshielded due to the resonance of amide functional group. In the compounds **3e-g**, the chemical shifts of thioxo carbon at C-3 were found to be at δ 176.79-177.53. From the above values it is clear that the replacement of a carbonyl group by a thiocarbonyl group results in a

Table-1: ^{1}H NMR spectral data of the compounds 3a-g (δ in ppm, *J* in Hz)



3a-g

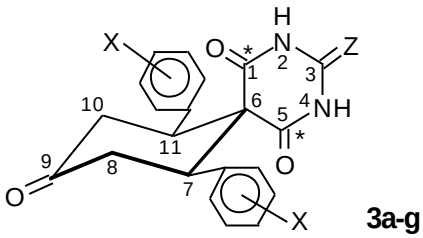
Protons	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
2-H*	11.84	11.50	11.35	11.18	12.83	12.05	12.34
4-H*	11.09	11.00	11.13	11.04	12.03	11.89	12.14
Aromatic	7.19-7.14	7.20-7.00	6.95-6.61	6.94-6.56	7.19-7.13	6.95-6.67	7.14-7.26
7-H_{ax}, 11-H_{ax}	4.40	3.90	3.79	3.78	4.61	3.81	3.96
*J*aa	13.87	13.87	14.16	13.00	13.73	13.00	17.61
*J*ae	4.88	4.33	4.40	4.95	5.04	4.54	4.73
8-H_{ax}, 10-H_{ax}	3.22	3.50	3.52	3.57	3.19	3.57	3.59
*J*aa	14.34	14.95	14.16	14.41	14.40	14.35	14.95
*J*gem	15.02	15.43	15.14	16.50	14.88	16.50	15.10
8-H_{eq}, 10-H_{eq}	2.51	2.40	2.35	2.40	2.51	2.45	2.53
*J*ae	4.89	4.16	4.88	4.00	5.34	4.00	4.68
*J*gem	16.50	13.14	15.63	15.00	16.51	15.00	13.42
X	2.46 (2′-CH_3)	3.35 (4′-CH_3)	3.37 (4′-$[CH_3]_2N$)	3.88 (4′-OH)	2.30 (2′-CH_3)	3.19 (4′-OH)	--- (4′-Cl)

* δ values of 2-H and 4-H are interchangeable

downfield shift[3,16]. For the compounds **3a-g**, the chemical shift values of the carbonyl carbon at position C-9 were highly deshielded (δ 205.79-209.44). This value is in good agreement with the ^{13}C NMR chemical shift of cyclohexyl methyl ketone[21]. The chemical shift values for carbonyl carbon at positions C-1 and C-5 were δ 167.91-175.00. The non-equivalences of these carbons are caused by the anisotrophy of the C-1 and C-5 carbonyl groups owing to the geometry of spiro structures[2].

In the compounds **3a-g**, the δ values of C-8 and C-10 showed peak at 44.05-48.76. For the compounds **3a** and **3e** the values were in the range of δ 44.05-44.38. The shielding of these carbons was due to electron releasing effects of methyl at *ortho*-position of the aryl rings. The chemical shift values of C-8 and C-10 (δ 44.05-48.76) of compounds **3a-g**, were slightly lower than those of C-7 and C-11 (δ 42.43-43.96). This is due to the electron-withdrawing effect of C=O group which is present next to them.

Table-2: ^{13}C NMR spectral data of the compounds 3a-g (δ in ppm)



3a-g

Carbons	3a	3b	3c	3d	3e	3f	3g
9-C	206.94	207.50	209.44	207.59	206.69	207.40	205.79
1-C*	171.75	171.00	173.48	171.99	170.46	169.98	169.17
5-C*	171.46	175.00	172.42	170.87	169.54	168.61	167.91
3-C	148.95	149.00	150.73	148.75	177.53	177.14	176.79
Aromatic	136.38 130.92 137.17 127.50 126.41 125.66	137.00 135.50 129.00 128.00	150.07 129.02 125.77 112.78	156.73 128.39 127.32 115.15	136.32 137.00 130.94 127.54 126.47 125.59	156.73 128.33 127.10 115.21	135.34 133.18 129.07 128.44
6-C	56.45	59.50	59.73	59.45	57.04	59.96	59.01
8, 10-C	44.05	48.50	48.31	48.37	44.38	48.76	48.57
7, 11-C	43.88	42.50	43.36	43.00	43.96	43.11	42.43
X	20.40 (2′-CH_3)	20.50 (4′-CH_3)	52.18 (4′-$[CH_3]_2N$)	--- (4′-OH)	20.45 (2′-CH_3)	--- (4′-OH)	--- (4′-Cl)

* δ values of 1-C and 5-C are interchangeable

The ^{13}C shifts of carbons of aromatic rings are assigned on the basis of the correlation chart of ^{13}C NMR spectral data available in the literature[19]. The spiro carbon C-6 of the compounds **3a-g** showed chemical shift values at δ 56.45-59.96 which are similar to the literature values[23]. The value for chloro-carbon in the aromatic ring for the compound **3g** was observed at δ 133.18.

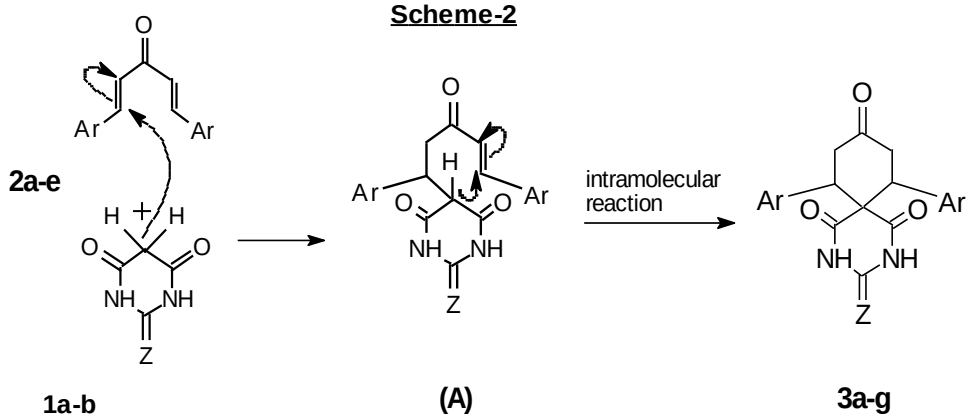
The high resolution mass spectra of the compounds **3a-g** showed peaks for their respective molecular ions (M^+) at m/z 390.2, 390.11, 448.3, 394.19, 406.25, 410.19 and 447.14 respectively. The isotopic pattern for Cl atom (^{35}Cl/^{37}Cl, 3:1) was observed in the molecular mass of **3g**. In **3g** the peak for M^+ was 447.14 (19%) and that for M^++2 was 449.12 (7%). From the fragmentation pattern in these spectra it is observed that most of

the prominent peaks were formed due to loss of CO, CONH/CSNH, substituted phenyl, tropylium, styryl, methyl, and keten fragments. This is in conformity with the mass spectral fragmentation pattern of those as reported before for 7,11-diphenyl-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraones. [3, 7, 16]

The ^{1}H NMR spectral data of the compounds **3a-g** clearly point to a rigid diarylcyclohexanone ring in which the two *aryl* groups adopt equatorial positions showing that they are *cis*-oriented. The difference between the stereochemical environments between the two amido groups in the pyrimidine structure is reflected both in their ^{1}H and ^{13}C NMR spectra[3, 7, 16] where the chemical shifts of the NH protons and the carbonyl carbons were found to be different. This can be understood by a rectangular placement of the ureide ring and the cyclohexanone ring due to the *cis*-arrangement of the two substituted aromatic rings. We, however, could not isolate any *trans*-isomer of any of the aforementioned spiro compounds.

The formation of these spiro compounds may be explained by an initial adduct (**A**) (Scheme-2) undergoing subsequent cyclization leading to the compounds **3a-g**.

Scheme-2



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