Cyclization of Diketones to Pyridazine and Furan Derivatives

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Condensation of (±)-2,3-bis(3,4-dimethoxybenzoyl)butane-1,4-dione **1** with different hydrazine bases afforded the corresponding pyridazines **2** and **3**. Refluxing the diketone **1** with methanolic hydrogen chloride yielded the corresponding 3,4-dimethylfuran derivative **5**. Reaction of acetonylacetone **6** with *p*-sulfamylphenylhydrazine afforded the corresponding 3,6-dimethyl-1*H*-pyridazine derivative **7**. Reaction of **7** with the appropriate isocyanate and isothiocyanate yielded the corresponding benzenesulfonylurea **8** and thiourea **9** derivatives respectively. The structures of the compounds synthesized were affirmed by microanalyses and spectral studies.

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Reaction of (±)-2,3-bis(3,4-dimethoxybenzoyl)butane-1,4-dione **1** with hydrazine hydrate, methylhydrazine and phenylhydrazine bases afforded the corresponding 4,5-dimethyl-3,6-(3,4-dimethoxyphenyl)-1,2-pyridazine derivatives **2**, **3a**, and **3b**, respectively. The ir spectra of the pyridazines **2** and **3** showed a strong absorption band at 1600 cm^{-1} for the C=N group. The symmetrical nature of the pyridazine **2** was clearly proven by the ^1H nmr spectrum which showed a singlet of six protons at δ 1.0 for the 2 methyl groups, as well as a quartet of two protons at δ 3.1 for the methine protons. This spectral pattern excluded the possibility of the pyridazine structure **2'a**.

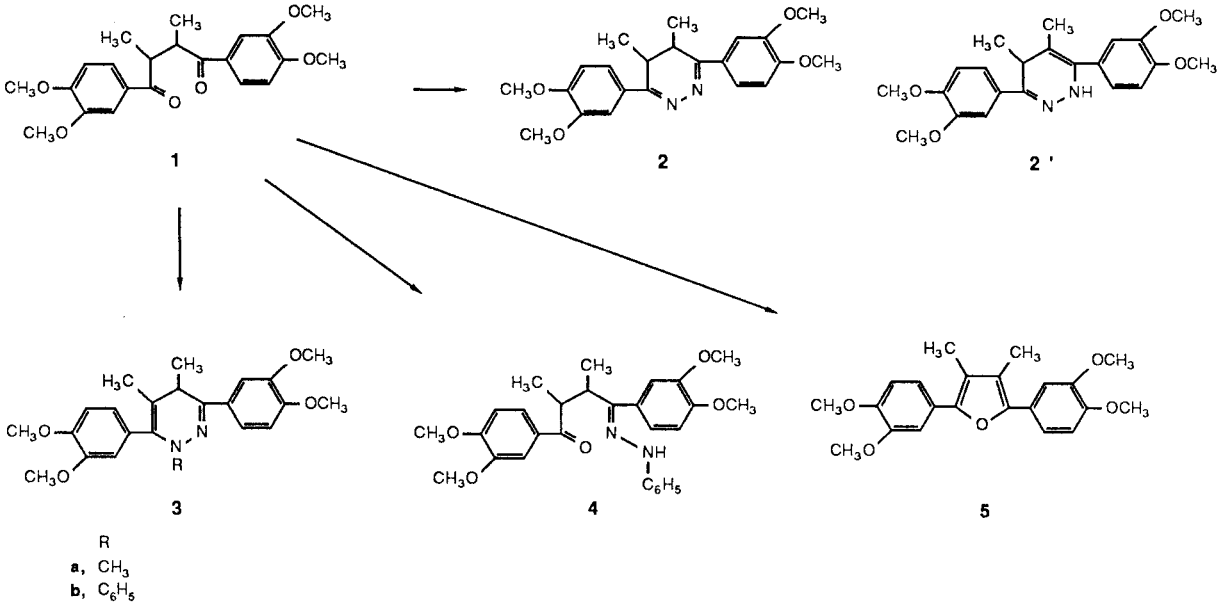
The ^1H nmr spectra of the pyridazine derivatives **3** showed a doublet (J = 4 Hz) at δ 1.2-1.4 for the CH_3-CH, and a singlet at δ 1.6 for the $CH_3C=$. The methine protons appeared as a quartet of one proton at δ 3.4-3.5.

The structures of pyridazine **2** was further affirmed by its mass spectrum analysis, which follow the common pathway for pyridazines [1]. It shows a strong molecular ion peak at m/e 382 while the above peak ($M-CH_3$) appeared at m/e 367. Other common prominent peaks in this spectrum were observed at m/e 352, 351, 335, 323, 307, 218, 187, 55, and 50.

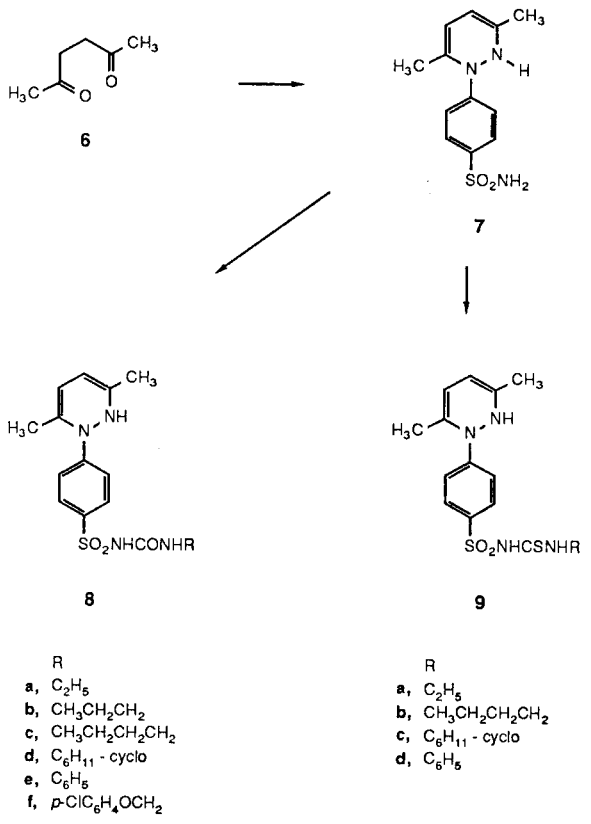
Heating the diketone **1** with phenylhydrazine on a steam bath for one hour afforded the corresponding phenylhydrazone **4**. In agreement with the suggested structure, the ir spectrum of **4** showed a strong carbonyl band at 1665 cm^{-1}, as well as a C=N and NH absorptions at 1595 and 3320 cm^{-1} respectively. The ^1H nmr spectrum of **4** showed in addition to the aromatic protons (m) at δ 6.7-7.9, two other multiplets at δ 1.5 and 3.7 for the methyl and methine protons respectively, and a methoxyl singlet at δ 4.1.

Refluxing the diketone **1** with 5% methanolic hydrogen

Scheme I



Scheme II



chloride for one hour, afforded 2,5-bis-(3,4-dimethoxyphenyl)-3,4-dimethylfuran **5**. This furan derivative is the key intermediate for the synthesis of the legnans galbelgin and veraguensin. The ^{1}H nmr showed the following signals at δ 2.4 (6H, s, $2CH_3$), δ 4.0 (12H, s, ArOMe), and δ 7.1-7.4 (6H, m, ArH).

Trials to cyclize the diketone **1** with *p*-sulfamylphenylhydrazine were unsuccessful. Probably because of low basicity or steric factors.

On the other hand, condensation of acetonylacetone with *p*-sulfamylphenylhydrazine afforded the pyridazine derivative **7**. The ir spectrum of **7** revealed two absorption bands at 1350 and 1185 cm^{-1} for $>NSO_2$, as well as an NH absorption at 3090 cm^{-1}. The NH_2 bands at 3220 and 3315 cm^{-1}. The ^{1}H nmr spectrum exhibited the following signals at δ 2.1 (6H, s, $2CH_3$), δ 5.8 (2H, q, CH), δ 5.1 (2H, s(b), NH_2), δ 7.0 (1H, s(b), NH). The two doublets (J = 4 Hz) at δ 6.5 and 7.8 represent H-2′ and H-3′ of the phenyl ring.

Substituted benzenesulfonylurea **8** and thiourea **9** derivatives were prepared by treatment of the pyridazine sulfonamide derivative **7** with the appropriate isocyanate and isothiocyanate derivatives respectively in dry acetone.

The ir spectra of these compounds revealed two absorption bands at 1330-1350 and 1170-1190 cm^{-1} indicative of the $>NSO_2$ group. A band at 1650-1660 cm^{-1} indicative for the urea carbonyl and a band at 1050-1100 cm^{-1} indicative for the thiourea carbonyl. The ^{1}H nmr spectra (Table 4) of the above compounds **8** and **9** show besides the R-protons the following signals at δ 1.9-2.1 (6H, s, $2CH_3$), δ 5.5-5.7 (2H, s, H-4 & H-5 of pyridazine), two doublets (J = 4 Hz) at δ 6.6-6.7 and 8.0-8.3 for H-2′ and H-3′ of the phenyl ring respectively. The ^{13}C nmr (Table 5) of the above compounds **8** and **9** showed the expected number of signals corresponding to each compound as well as a carbonyl signal at δ 169.8-170.4 for compounds **8** and a thiocarbonyl signal at 181.6-182.1 for compounds **9**.

Table 1

Analytical Data of Pyridazine Derivatives

Compound No.	Yield %	Mp °C	Formula	Calcd. %/Found % C	H	N
2	70	148	$C_{22}H_{26}N_2O_4$	69.1	6.8	7.3
				69.0	6.7	7.2
3a	75	150	$C_{23}H_{28}N_2O_4$	69.6	7.1	7.1
				69.5	7.0	7.2
3b	55	222	$C_{28}H_{30}N_2O_4$	73.3	6.6	6.1
				73.3	6.5	6.1
7	85	128	$C_{12}H_{15}N_3O_2S$	54.3	5.7	15.8
				54.3	5.6	15.9

EXPERIMENTAL

The ^{1}H nmr spectra were recorded with a Varian EM 360L spectrometer using tetramethylsilane as internal standard. The ^{13}C nmr spectra were recorded on Joel JNM-FX 100 NMR spectrometer. The ir spectra were obtained using sodium chloride plates on Perkin-Elmer 297 spectrometer as solutions in bromoform. Mass spectra were recorded on a Kratos MS 30. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. All temperatures are °C.

3,4-Dimethoxypropiophenone [1].

A mixture of veratrol (22 g), polyphosphoric acid (44 g) and propionic acid (35 ml) was stirred and heated at 100° for 90 minutes. The reaction mixture was cooled, diluted with water and extracted with ether. The etherial extract was partitioned with 5% sodium hydroxide solution, washed with water and dried over anhydrous sodium sulfate. The ketone was obtained as crystalline solid from ether in 75% yield, tlc system: silica, 5% acetone:benzene, mp 57,5°, bp 157-160° at 5 mm Hg.

α-Bromo-3,4-dimethoxypropiophenone [2].

Bromine (9.3 ml), in chloroform (30 ml), was added gradually with stirring, to a solution of 3,4-dimethoxypropiophenone (32.5 g) in chloroform (150 ml). The mixture was set aside for 4 hours, with occasional agitation. Evaporation of the washed (sodium bicarbonate solution and water) and dried (magnesium sulfate), chloroform solution left a brownish oil, which on being triturated with ether, and diluted with three times its volume of petroleum ether (40-60°) afforded the bromoketone as almost white feathry needles (30 g, 88%) mp 88°. Concentration of the mother liquor gave a further 2.4 g of the product.

(±)-2,3-Bis(3,4-dimethoxybenzoyl)-butane-1,4-dione [3].

To liquid ammonia (50 ml) was added ferric chloride (25 mg) followed by sodium (400 mg) and the mixture stirred until disappearance of the

Table 2

^{1}H NMR Spectral Data of Pyridazines [a]

Compound	CH_3-CH- (3H, d) J = 4	CH_3-C≡ (3H,s)	CH (1H, q) J = 4	OCH_3 (12H, s)	ArH (6H, m)	Others
2	1.0 [b]		3.1 [c]	4.0	7.0-8.0	
3a	1.2	1.6	3.5	3.9	6.9-7.7	3.1 (CH_3N)
3b [d]	1.4	1.6	3.4	3.9	6.8-7.8 [e]	
7		2.1 [f]	5.8 [g]		6.5-7.8 [h]	5.1 (2H, NH_2)

[a] Solutions in deuteriochloroform, δ in ppm, J = coupling constant in Hz. [b] 6H ($2CH_3$). [c] 2H. [d] Solution in deuterated dimethylsulfoxide. [e] 2 m (11H). [f] 6H ($2CH_3$). [g] 2H (s, 2CH). [h] 2d (4H, J = 4).

blue color. The 3,4-dimethoxypropiophenone (2.6 g), was added with continued stirring for 15 minutes, followed by a molar equivalent amount of of α-bromo-3,4-dimethoxypropiophenone. After 90 minutes, ammonium chloride (3 g), and chloroform (50 ml) were added. The ammonia was allowed to evaporate, and the mixture filtered and the residue washed with chloroform (30 ml). The combined filtrate and washing was diluted with methanol and concentrated to yield (±)-2,3-bis-(3,4-dimethoxybenzoyl)-1,4-dione (90% yield), mp 165°.

Pyridazine Derivatives **2**,, **3**, and **7** (Tables 1, 2).

A solution of **1** or **6** (0.01 mole) in ethanol (25 ml), was refluxed with the proper hydrazine (0.01 mole) for 3-8 hours. The pyridazine derivatives were obtained in 55-85% yields after concentration and were recrystallized from ethanol in needles.

3,6-Dimethyl-2-(*p*-sulfamylphenyl)-1-hydropyridazine (**7**).

Compound **7** had ms: m/e (relative abundance), M^+ 382 (12.6), 379 (10), 368 (24), 367 (100), 352 (7), 351 (17), 336 (2), 335 (3), 323 (3), 322 (2), 309 (1), 232 (1), 219 (2), 218 (3), 194 (4), 183 (6), 182 (2), 166 (3), 165 (23), 163 (10), 148 (3), 92 (3), 79 (4).

(±)-2,3-Bis(3,4-dimethoxybenzoyl)butane-1-one-4-phenylhydrazone (**4**).

(±)-2,3-Bis(3,4-dimethoxybenzoyl)butane-1,4-dioxane (0.4 g, 0.001 mole) in ethanol (20 ml), was refluxed on steam bath with phenylhydrazine (0.13 g, 0.0012 mole) for one hour. The hydrazone was obtained in 75% yield (0.37 g) after concentration, and was recrystallized from methanol in yellow needles, mp 140°; ir (bromoform): 1665 (C=O), 1595 (C=N), 3320 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.5 (m, 6H, $2CH_3$), 3.7 (m, 2H, CH), 4.1 (s, 12H, OCH_3), 6.7-7.9 (m, 12H, ArH + NH).

Anal. Calcd. for $C_{28}H_{32}N_2O_5$: C, 70.5; H, 6.7; N, 5.9. Found: C, 70.4; H, 6.6; N, 5.7.

2,5-Bis-(3,4-dimethoxyphenyl)-3,4-dimethylfuran (**5**) [3,4].

The diketone **1** (135 mg) was refluxed in methanolic hydrogen chloride (2.5 ml), for one hour. The furan separated out from the mixture (105 mg, 80%) was recrystallized from methanol as fluorescent needles mp 177°; ir (bromoform): 1605 cm^{-1} (C=C); ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 6H, $2CH_3$), 4.0 (s, 12H, OCH_3), 7.1-7.4 (m, 6H, ArH); ^{13}C nmr (deuteriochloroform): δ 16.5 (CH_3), 55.9 (OCH_3), 110.7, 112.9, 122.3, 130.4, 134.8, 148.8, 149.3, 157.6 (aromatic C).

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.7; H, 6.5. Found: C, 71.5; H, 6.6.

Substituted *p*-(3,6-dimethyl-1-hydropyridazine-2)benzenesulfonylurea Derivatives **8** (Tables 3, 4 and 5).

A mixture of **7** (8 g, 0.03 mole) and anhydrous potassium carbonate (10 g, 0.01 mole) in dry acetone (100 ml), was stirred and refluxed for 1.5 hour. At this temperature, a solution of the appropriate isocyanate (0.075 mole) in dry acetone (20 ml), was added dropwise. After the mixture was stirred and refluxed overnight, acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with 2*N* hydrochloric acid and purified by recrystallization from the appropriate solvent.

Table 3

Substituted *p*-(3,6-Dimethyl-1-hydropyridazine-2)benzenesulfonylurea and Thiourea Derivatives

Compound No.	Yield %	Mp °C	Formula	Calcd. %/Found % C	H	N
8a	70	134	$C_{15}H_{20}N_4O_3S$	53.6	6.0	16.9
				53.5	6.1	17.0
8b	65	143	$C_{16}H_{22}N_4O_3S$	57.7	6.3	16.0
				57.4	6.2	15.9
8c	60	158	$C_{17}H_{24}N_4O_3S$	56.0	6.6	15.4
				56.2	6.5	15.5
8d	78	230	$C_{19}H_{26}N_4O_3S$	58.4	6.6	14.3
				58.5	6.5	14.2
8e	72	272	$C_{19}H_{20}N_4O_3S$	59.3	5.3	14.3
				59.4	5.5	14.1
8f	62	163	$C_{20}H_{21}ClN_4O_4S$	53.5	4.7	15.3
				53.4	4.8	15.3
9a	65	105	$C_{15}H_{20}N_4O_2S_2$	51.1	5.9	15.9
				51.0	6.0	16.0
9b	72	110	$C_{17}H_{24}N_4O_2S_2$	53.6	6.3	14.7
				53.5	6.3	14.8
9c	70	122	$C_{19}H_{26}N_4O_2S_2$	56.1	6.4	13.9
				56.0	6.5	14.0
9d	75	260	$C_{19}H_{20}N_4O_2S_2$	57.0	5.0	14.0
				56.9	5.1	14.0

Substituted *p*-(3,6-Dimethyl-1-hydropyridazine-2(benzenesulfonylthiourea Derivatives **9** (Tables 3, 4 and 5).

A mixture of the pyridazine **7** (8 g, 0.03 mole) and anhydrous potassium carbonate (10 g, 0.01 mole) in dry acetone (100 ml) was stirred and treated with the appropriate isothiocyanate (0.05 mole). After the mixture was refluxed and stirred for 10 hours, acetone was removed under reduced pressure. The solid mass thus obtained was dissolved in water and acidified with 2*N* hydrochloric acid. The crude product was purified by recrystallization from the appropriate solvent.

Table 4

^{1}H NMR [a] Spectral Data of Benzenesulfonylurea and Thiourea Derivatives

Compound No.	Phenyl H-2′ (2H, d, J = 4)	Protons H-3′ (2H, d, J = 4)	Pyridazine H H-4 and H-5 (2H, s)	CH_3 (6H, s)	Others
8a	8.2	6.6	5.7	2.0	7.0 (3H, NH, m), 4.0 (2H, CH_2, q, J = 4), 1.3 (3H, CH_3, t, J = 4)
8b	8.3	6.7	5.7	1.9	6.9 (3H, NH, m), 3.9 (2H, CH_2, t, J = 3), 1.9 (2H, CH_2, m), 1.2 (3H, CH_3, t, J = 3)
8c	8.1	6.6	5.6	2.0	6.8 (3H, NH, m), 3.9 (2H, CH_2, t, J = 3), 1.6 (4H, CH_2, m), 1.3 (3H, CH_3, t, J = 3)
8d	8.0	6.6	5.6	2.1	6.9 (3H, NH, m), 1.8-2.3 (11H, m, cyclohexyl)
8e	8.2	6.7	5.5	2.0	7.4 (5H, Ph, s), 7.0 (3H, NH, m)
8f	8.1	[b]	5.6	2.1	6.7-7.9 (6H, m), 6.9 (3H, NH, m), 5.4 (2H, CH_2, s)
9a	8.0	6.6	5.6	1.9	6.9 (3H, NH, m), 4.0 (2H, CH_2, q, J = 4), 1.3 (3H, CH_3, t, J = 4)
9b	8.0	6.7	5.7	1.9	6.8 (3H, NH, m), 4.0 (2H, CH_2, t, J = 3), 1.9 (2H, CH_2, m), 1.2 (3H, CH_3, t, J = 3)
9c	7.9	6.6	5.7	2.0	6.9 (3H, NH, m), 3.9 (2H, CH_2, t, J = 3), 1.7 (4H, CH_2, m), 1.2 (3H, CH_3, t, J = 3)

[a] Solutions in deuterated dimethylsulfoxide, δ in ppm, J = Coupling constant in Hz. [b] Overlap with R protons.

Table 5

^{13}C NMR Spectral Data of Benzenesulfonylurea and Thiourea Derivatives [a]

Compound No.	Aromatic C	CO/CS	CH_3	R-C
8a	150.8, 130.8, 127.6, 126.9, 114.5, 103.8	170.4	11.1	30.8 (CH_2), 13.4 (CH_3)
8b	151.3, 129.4, 127.7, 127.0, 113.5, 104.0	170.0	10.9	52.1, 29.4, 11.8 (Pr C)
8c	151.2, 130.3, 127.8, 124.9, 103.7	169.8	11.3	55.4, 30.3, 17.1, 11.2 (Bu C)
8e	150.0, 141.3, 135.7, 128.9, 127.9, 127.0, 121.2, 120.1, 109.5, 103.4	170.1	11.1	
8f	150.5, 144.3, 130.2, 129.4, 127.7, 126.8, 121.1, 116.7, 114.4, 103.2	170.2	12.0	64.5 (CH_2)
9a	150.3, 132.6, 127.8, 127.4, 113.1, 103.8	182.1	11.3	32.1 (CH_2) 13.6 (CH_3)
9b	151.3, 130.6, 127.7, 127.0, 112.8, 103.6	181.9	10.8	55.3, 30.4, 17.2, 11.3 (Bu C)
9d	150.1, 141.3, 135.7, 129.0, 127.9, 127.0, 121.2, 120.1, 109.5, 103.4	181.6	11.1	

[a] Solutions in deuterated dimethylsulfoxide, δ in ppm.

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