Synthesis and Reactions of 1-Heteroaryl-5-phenyl-4-pentyne-1,3-diones

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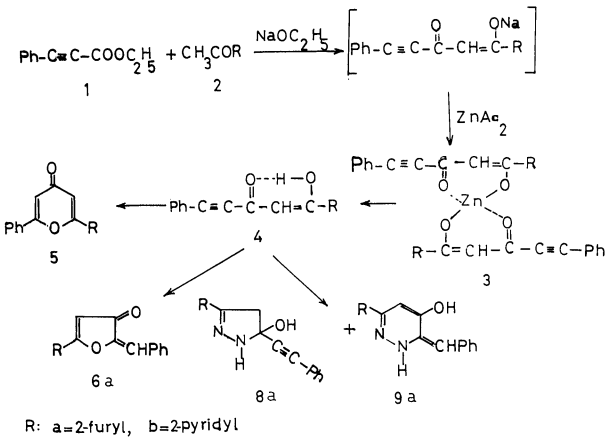
Synopsis. The synthesis of the title acetylenic β-diketones which are starting materials to prepare cyclic and bicyclic compounds is described.

In continuation of our studies of the chemistry of acetylenic β-diketones,[1,2] we have synthesized the title compounds using the method reported by our group[3] which is found to give better yields than the previously reported methods.[4,5]

This simple and convenient method is easily performed in dry ether at 0 °C by stirring a mixture of ethyl phenylpropiolate (**1**) and 2-acetylfuran (**2a**) or 2-acetylpyridine (**2b**) in a 1 : 1 molar ratio using sodium ethoxide as base for a period of 3 h. The reaction mixture was treated with aqueous zinc acetate, and the separated zinc salts **3a,b** were subsequently decomposed on treatment with hydrochloric acid to give the corresponding 1-substituted 5-phenyl-4-pentyne-1,3-diones **4a,b** (Scheme 1).



Scheme 1.

The structure of these acetylenic β-diketones **4a,b** were elucidated from their spectral and analytical data (Tables 1, 2). A sharp absorption in the range 2204—2205 cm^{-1}, consistent with the presence of an acetylenic

Table 1. The IR and ^1H NMR Spectral Data of Acetylenic β-Diketone and 4*H*-Pyran-4-one Derivatives

Compound	IR (KBr)		NMR		Solvent
	cm^{-1}	ν	δ	Protons[a]	
3a	1578	C=O			
	2204	C≡C			
3b	1585	C=O			
	2206	C≡C			
4a	1581	C=O	5.98(s)	CH=	DMSO-d_6
	2205	C≡C	8.00(s)	C=COH	
	3485(br.)	OH			
4b	1589	C=O	6.20(s)	CH=	DMSO-d_6
	2204	C≡C	8.70(s)	C=COH	
	3521(br.)	OH			
5a	1624, 1660	C=O	6.73(d)	$H_{3,5}$	$CDCl_3$
5b	1617, 1649	C=O	6.68(d)	$H_{3,5}$	$CDCl_3$
6a	1642	PhCH=C	6.45(s)	H_4	DMSO-d_6
	1689	C=O	7.28(s)	PhCH=	
7a	1347, 1534	NO_2	6.48(s)	H_5	DMSO-d_6
	1642	C=O			
8a	1645	C=N	4.15(q)	CH_2	DMSO-d_6
	2205	C≡C	6.35(br.)	OH	
	3526(br.)	OH			
9a	1645	C=N	5.69(s)	H_4	DMSO-d_6
	1652	PhCH=C	5.88(br.)	OH	
	3489(br.)	OH	6.69(s)	PhCH=	
10a	1610	C=N(ring)	3.53, 3.75(s)	$2CH_2$	DMSO-d_6
	1639	C=N(oxime)	10.60(s)	OH	
	3395(br.)	OH	11.35(s)	OH(oxime)	
11a	1609	C=N(ring)	4.05(s)	CH_2	DMSO-d_6
	1621	C=N(oxime)	6.60(s)	H_4	
	3479(br.)	OH	11.60(s)	OH	
12a	1074	C=S	7.85, 8.10(s)	$2H_{3,4}$	$CDCl_3$
13a	1082	C=S	(b)		$CDCl_3$
14a	1659	C=N	6.60(d)	H_3	$CDCl_3$
	3525(br.)	OH	6.72(d)	H_5	
15a	1074	C=S	3.35(s)	N-CH_3(b)	$CDCl_3$
16a	1646	C=O	6.58(d)	$2H_{3,5}$	$CDCl_3$

a) s: Singlet. d: Doublet. g: Quartet. All OH protons are exchanged with deuterium oxide.
b) $H_{3,5}$ signals are overlapped by the aromatic protons multiplet.

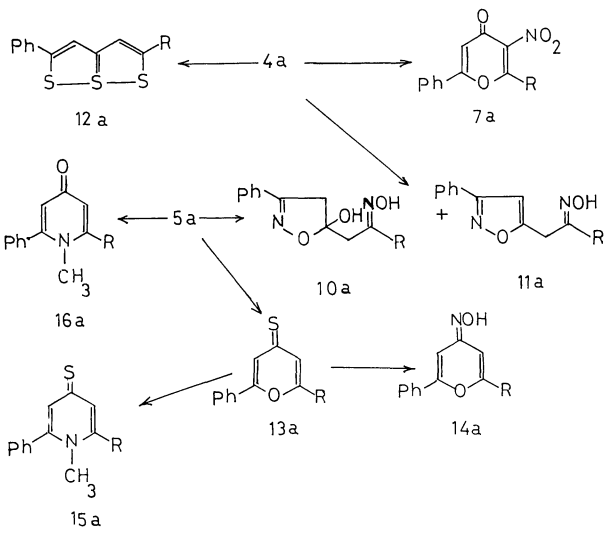
Table 2. Analytical Data of Acetylenic β-Diketone and 4*H*-Pyran-4-one Derivatives

Compd No.	Mp °C	Yield %	Crystallization solvent	Formula	Analysis/% Calcd (Found) C	H	N	S
3a	162	83	MeOH	$C_{30}H_{18}O_6Zn$	66.8 (66.8	3.3 3.4)		
3b	145	81	MeOH	$C_{32}H_{20}N_2O_4Zn$	68.4 (68.5	3.6 3.4	5.0 4.9)	
4a	181	46	MeOH	$C_{15}H_{10}O_3$	75.6 (75.3	4.2 4.4)		
4b	168	41	MeOH	$C_{16}H_{11}NO_2$	77.1 (77.3	4.4 4.1	5.6 5.5)	
5a	130	62	MeOH	$C_{15}H_{10}O_3$	75.6 (75.5	4.2 4.3)		
5b	136	56	MeOH	$C_{16}H_{11}NO_2$	77.1 (77.3	4.4 4.4	5.6 5.4)	
6a	>300	41	Benzene–methanol	$C_{15}H_{10}O_3$	75.6 (75.5	4.2 4.1)		
7a	195	78	MeOH	$C_{15}H_9NO_5$	63.6 (63.8	3.1 2.9	4.9 4.7)	
8a	147	33	MeOH	$C_{15}H_{12}N_2O_2$	71.4 (71.6	4.7 4.6	11.1 10.8)	
9a	285	39	EtOH	$C_{15}H_{12}N_2O_2$	71.4 (71.3	4.7 4.9	11.1 11.4)	
10a	163	32	Benzene–petroleum	$C_{15}H_{14}N_2O_4$	62.9 (62.6	4.8 4.9	9.8 9.6)	
11a	139	43	MeOH	$C_{15}H_{12}N_2O_3$	67.1 (67.3	4.5 4.4	10.4 10.1)	
12a	152	73	Benzene–petroleum	$C_{15}H_{10}OS_3$	59.6 (59.6	3.3 3.1		31.7 31.5)
13a	98	86	MeOH	$C_{15}H_{10}O_2S$	70.8 (70.7	3.9 3.8		12.6 12.7)
14a	133	93	MeOH	$C_{15}H_{11}NO_3$	71.1 (70.9	4.3 4.3	5.5 5.6)	
15a	168	86	EtOH	$C_{16}H_{13}NOS$	71.9 (71.7	4.8 4.9	5.2 5.1	11.9 11.7)
16a	146	88	MeOH	$C_{16}H_{13}NO_2$	76.5 (76.4	5.2 5.2	5.6 5.5)	

linkage, indicating that the reaction pathway proceeds through a Claisen condensation, while the ^{1}H NMR (enolic proton at δ=8.00—8.70) and IR (broad absorption 3485—3521 cm^{-1}) data proved that the system was more strongly enolized than 1-aryl-5-phenyl-4-pentyne-1,3-diones reported before.[3] The compounds **4a,b** gave a positive iron(III) chloride test and easily formed metal chelates.

The cyclization of **4a** to 2-(2-furyl)-6-phenyl-4*H*-pyran-4-one (**5a**) has been achieved by heating, while its conversion into 2-benzylidene-5-(2-furyl)-3(2*H*)-furanone (**6a**) alongside with **5a** was carried out in refluxing ethanol. However, **4b** could be cyclized to its pyrone **5b** on reaction with hydrochloric acid. On the other hand, treatment of **4a** with a mixture of nitric and sulfuric acids gave 2-(2-furyl)-3-nitro-6-phenyl-4*H*-pyran-4-one (**7a**) (Scheme 2). It is reported that the ^{1}H NMR spectra of the 2,6-diaryl-4*H*-pyran-4-ones gave a singlet of two protons at δ=6.67—6.92 for $H_{3,5}$ of the pyrone ring.[3] However, the spectra of **5a,b** showed a doublet at δ=6.68—6.73 for the $C_{3,5}$ ring protons (Table 1).

The reaction of 1-(2-furyl)-5-phenyl-4-pentyne-1,3-dione (**4a**) with hydrazine hydrate led to the formation of a mixture of 3-(2-furyl)-5-hydroxy-5-phenylethynyl-2-pyrazoline (**8a**) and 3-benzylidene-6-(2-furyl)-2,3-dihydro-4-pyridazinol (**9a**) (Scheme 1). However, 5-aryl-3-(1-hydrazono-2-phenylethyl)-1*H*-pyrazoles were



Scheme 2.

reported to be formed by the reaction of 1,5-diaryl-4-pentyne-1,3-diones with hydrazine hydrate under the same conditions.[3] The ^{1}H NMR spectra of **8a** exhibited, besides other characteristic signals, a quartet at δ=4.15 for the methylene protons, and the exchangeable proton at δ=6.35 for OH, while the pyridazinol **9a** gave two singlets at δ=5.69 and 6.69 for the H_4 pyridazine ring and benzylidene protons, respectively (Table 1).

The reaction of 1,5-diaryl-4-pentyne-1,3-diones or 2,6-diaryl-4*H*-pyran-4-ones with hydroxylamine hydrochloride in pyridine leads to isoxazole derivatives,[6] while in ethanol 2-isoxazolines are formed.[7] In the present work, treatment of **4a** or **5a** with hydroxylamine hydrochloride in pyridine afforded a mixture of 5-hydroxy-5-[2-hydroxyimino-2-(2-furyl)ethyl]-3-phenyl-4,5-dihydroisoxazole (**10a**) and 5-[2-hydroxyimino-2-(2-furyl)ethyl]-3-phenylisoxazole (**11a**). The product **10a** was converted to **11a** by heating in xylene (Scheme 2). The structures of the compounds **10a** and **11a** are consistent with the IR and ^{1}H NMR data and elemental analysis (Tables 1, 2). Also, the electronic spectrum of **11a** gave an absorption maximum at 254 nm (ε 10222) almost in the same region reported for 3-phenylisoxazoles.[6] Moreover, they are in good agreement with those earlier reported.[6-8]

Treatment of **4a** and **5a** with phosphorus pentasulfide afforded 2-(2-furyl)-5-phenyl-6-thiathiophthene (**12a**) and 2-(2-furyl)-6-phenyl-4*H*-pyran-4-thione (**13a**), respectively. The thione **13a** was converted into the oxime **14a** and 1-methyl-4(1*H*)-pyridinethione **15a** on reactions with hydroxylamine and aqueous methylamine, respectively, while 1-methyl-4(1*H*)-pyridone **16a** was formed from **5a** and aqueous methylamine (Scheme 2, Table 1).

Experimental

General Methods. Microanalyses were performed by the Microanalysis Unit, Cairo University, Cairo. IR spectra were measured with a Unicam, SP 1025 spectrophotometer for potassium bromide pellets. The ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer with TMS as internal standard.

Preparation of 1-Substituted 5-phenyl-4-pentyne-1,3-diones 4a,b (Tables 1, 2). An ethereal solution of the ketone **2a**,**b** (0.0862 mol) and ethyl phenylpropiolate (**1**) (0.0862 mol) were successively added to an ice-cold suspension of sodium ethoxide (2.0 g. 0.0289 mol) in dry ether (150 ml). The reaction mixture was stirred at 0 °C for 3 h and then poured into 5% aqueous ice-cold zinc acetate solution (100 ml). The precipitated zinc salts **3a**,**b** were filtered, washed with ether, and dried. A suspension of the crude zinc salts in ether (120 ml) was stirred with 2—4% hydrochloric acid (400 ml) for 6 h. The ethereal solution after washing with 10% sodium hydrogen carbonate, drying (anhydrous sodium sulfate), and evaporation afforded the acetylenic β-diketones **4a**,**b** which crystallized from methanol as pale brown needles.

Conversion of 4a to 2-(2-Furyl)-6-phenyl-4*H*-pyran-4-one (5a) (Tables 1, 2). The compound **4a** was heated in an oil bath for 5—10 min just above its melting point, then extracted with ether. Filtration, followed by recrystallization from methanol gave **5a** as yellow needles.[4]

Action of Hydrochloric Acid on 4b (Tables 1, 2). A solution of **4b** (0.0034 mol) in methanol (10 ml) was refluxed with concentrated hydrochloric acid (1 ml) for 2 h. After concentration and cooling, the pyrone **5b** separated out which was crystallized from methanol as pale yellow needles.

5-(2-Furyl)-2-benzylidene-3(2*H*)-furanone (6a) (Tables 1, 2). This compound was prepared alongside with **5a** by refluxing of the acetylenic β-diketone **4a** in ethanol as described earlier.[9]

2-(2-Furyl)-3-nitro-6-phenyl-4*H*-pyran-4-one (7a) (Tables 1, 2). This compound was prepared from **4a** and a mixture of concentrated nitric (*d* 1.41; 2 ml) and sulfuric (*d* 1.84; 2 ml) acids in glacial acetic acid (6 ml) as described earlier.[10]

3-(2-Furyl)-5-hydroxy-5-phenylethynyl-2-pyrazoline (8a) and 3-Benzylidene-6-(2-furyl)-2,3-dihydro-4-pyridazinol (9a) (Tables 1, 2). A suspension of **4a** (0.0012 mol) in ethanol (20 ml) was stirred at room temperature with 99% hydrazine hydrate (1 ml; 0.020 mol) for 3 h. After removal of most of the solvent under reduced pressure, the separated solid was subjected to fractional crystallization from methanol. The pyrazoline **8a** separated first, and from the mother liquor, pyridazinol **9a** was obtained.

5-Hydroxy-5-[2-hydroxyimino-2-(2-furyl)ethyl]-3-phenyl-4,5-dihydroisoxazole (10a) and 5-[2-Hydroxyimino-2-(2-furyl)ethyl]-3-phenylisoxazole (11a) (Tables 1, 2). A solution of **4a** or **5a** (0.0029 mol) in pyridine (20 ml) was refluxed with hydroxylamine hydrochloride (0.011 mol) for 3 h. After removal of most of the solvent under reduced pressure, water (10 ml) was added, and the separated solid was subjected to fractional crystallization from chloroform. The dihydroisoxazole **10a** separated first, and from the mother liquor, isoxazole **11a** was obtained.

2-(2-Furyl)-6-phenyl-4*H*-pyran-4-thione (13a) (Tables 1, 2). This compound was prepared from 2-(2-furyl)-6-phenyl-4*H*-pyran-4-one (**5a**) and phosphorus pentasulfide as described earlier.[11]

Conversion of 5-Hydroxyisoxazole 10a to Isoxazole 11a. A solution of **10a** (0.0023 mol) in dry xylene (10 ml) was refluxed for 15 h. On concentration, the isoxazole **11a** (78% yield) separated out, and was crystallized from methanol.

2-(2-Furyl)-6-phenyl-4*H*-pyran-4-one Oxime (14a) (Tables 1, 2). This compound was prepared from 2-(2-furyl)-6-phenyl-4*H*-pyran-4-thione (**13a**) and hydroxylamine hydrochloride and sodium acetate in ethanol as described earlier.[11]

1-Methyl-4(1*H*)-pyridinethione (15a) and Pyridone (16a) (Tables 1, 2). These were prepared from the respective 4(1*H*)-pyranethione **13a** and pyrone **5a** and 33% aqueous methylamine solution as described earlier.[12]

2-(2-Furyl)-5-phenyl-6-thiathiophthene (12a) (Tables 1, 2). A solution of **4a** (0.004 mol) in dry benzene (30 ml) was refluxed with phosphorus pentasulfide (0.009 mol) for 1 h. The reaction mixture was worked up as described earlier.[11]

The isolated thiathiophthene **12a** was crystallized from benzene–petroleum as violet needles.

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