Synthesis and Reactions of 3-Iodo-4*H*-pyran-4-ones

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3-Iodo-4*H*-pyran-4-ones have been synthesised in excellent yield by the reaction of acetylenic β-diketones with iodine monochloride and were converted into the corresponding 4*H*-pyran-4-thiones. The iodopyrones and thiopyrones gave with methylamine the respective *N*-methylpyridones and thiopyridones. The structure of the above compounds was confirmed from their spectral characteristics.

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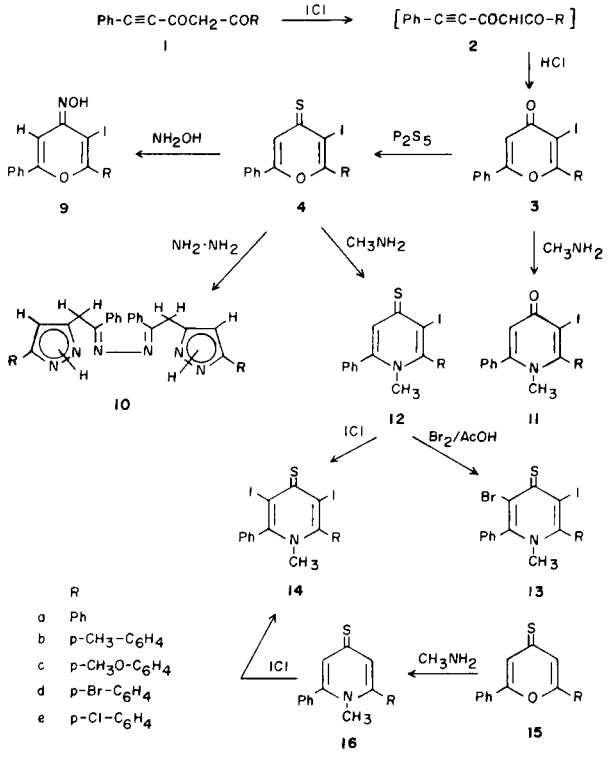
Halogen substituted 4*H*-pyran-4-ones are potential precursors of functional derivatives of biological interest. Thus, several iodo-4-pyridones are reported to be used for pharmaceutical purposes [1].

However, 4*H*-pyran-4-ones with nuclear halogen are not much studied in literature. In the present study, a simple method for the synthesis of 3-iodo-2,6-diaryl-4*H*-pyran-4-ones from acetylenic β-diketones is described. The latter compounds which are also versatile intermediates in the synthesis of several heterocyclic systems [2], were prepared by base catalysed condensation of acetylenic esters with suitable ketones [2].

Treatment of the acetylenic β-diketones **1a-e** with iodine monochloride gave the 2,6-diaryl-3-iodo-4*H*-pyran-4-ones **3a-e**. The reaction is assumed to proceed by intermediate formation of the 1,5-diarylpent-1-yne-4-iodo-3,5-diones **2a-e**, which are susceptible to cyclization to the corresponding 4*H*-pyran-4-ones **3** under the reaction conditions. Treatment of the latter with phosphorus pentasulphide afforded the corresponding 2-aryl-3-iodo-6-phenyl-4*H*-pyran-4-thiones **4a-e** (Scheme I).

Scheme I



The infrared spectra (Table 1) of the 3-iodo-2,6-diaryl-4*H*-pyran-4-ones gave the carbonyl absorption [3] at 1600-1624 cm^{-1}, while the thiopyrones **4a-e** exhibited the thiocarbonyl absorption at 1150-1155 cm^{-1}. The ^1H nmr spectra of the 3-iodopyrones (Table 1) gave a singlet at δ 6.77-6.97 for the H-5 proton almost in the same region reported for the respective 2,6-diaryl-4*H*-pyran-4-ones [2]. However, an appreciable deshielding for the H-5 proton is observed for 3-iodothiopyrones due to the presence of C=S group [4].

Table I

Infrared and ^1H NMR Spectral Data of the 3-Iodo-4*H*-pyran-4-ones and their Derivatives in Deuteriochloroform

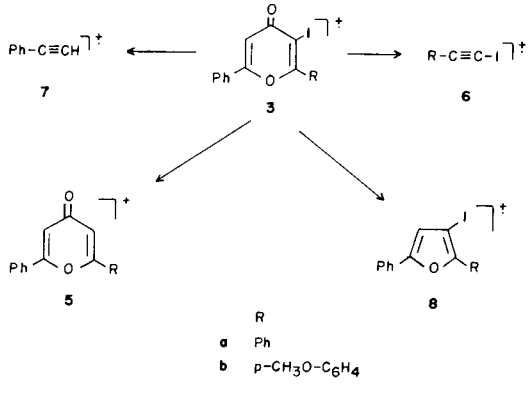
	IR (cm^{-1})			^1H NMR, δ [a]		
	C=S	C=O	C=N	OH	H-5 (s)	OH (s)
3a		1615			6.83	
3b		1600			6.97	
3c [b]		1619			6.77	
3d		1624			6.79	
3e [b]		1624			6.87	
4a	1157					
4b	1155					
4c	1150					
4d	1150					
4e	1153					
9a			1655	3230	6.99	11.04
9b			1653	3240	6.87	10.93
9c			1650	3230		
9e			1641	3220	6.90	11.00

[a] s: Singlet. [b] Spectra carried out in DMSO-d_6.

The mass spectra of the 2,6-diaryl-3-iodo-4*H*-pyran-4-ones **3a,c** (Scheme II) gave the molecular ion as the base

peak. A major fragmentation route involved loss of iodine giving the intense peak **5**. The ease of elimination of a halogen atom has been also reported in the mass spectra of other halo-heterocyclic systems like 3-bromo-2-pyrones [5], 2,5-dichlorothiophene [6] and 2,3,4-tribromopyrroles [7]. Similar to the parent 4*H*-pyran-4-ones, an important fragmentation process is the retro Diels-Alder reaction [8] which gave rise to the two species **6** and **7**. However, the ketene species expected to be formed in these reactions were not observed, a behaviour similarly reported for some other phenyl substituted 4*H*-pyran-4-ones [8]. Another fragmentation route is the expulsion of CO leading to the furan species **8** which gave rise to a series of peaks characteristic of furans [9].

Scheme II



The introduction of iodine atom in the 3 position of the pyrone ring greatly increased its stability. Thus, while 4-pyrones readily react with hydroxylamine to give hydroxy-pyridones [10] or isoxazoles [11], the 3-iodo derivatives **3c,e** were recovered unchanged on treatment with hydroxylamine in ethanol. However, similar treatment of the 3-iodothiopyrones **4a-c,e** led to the formation of the respective oximes **9a-c,e**. Their infrared spectra (Table I) exhibited a C=N band at 1641-1655 cm^{-1} as well as a broad OH at 3220-3240 cm^{-1}. Their ^1H nmr spectra showed the H-5 proton as a singlet at δ 6.87-6.99 as well as the OH proton at δ 10.93-11.04.

With hydrazine hydrate most of 4-pyrones give pyrazole derivatives [2,10b,12], *N*-aminopyridones [13] or pyrone hydrazones [14]. The reaction of the 3-iodo pyrones **3b, d,e** with hydrazine hydrate led to expulsion of the iodine giving the respective pyrones. However, the reaction of the 3-iodothiopyrones **4b,c** with hydrazine hydrate gave the pyrazole azines **10b,c** with the elimination of iodine atom (Scheme I). The infrared of the azines showed the characteristic bands (*cf.* Experimental). Their ^1H nmr spectra gave the exocyclic methylene protons at δ 4.38-4.63 and the pyrazole H-4 proton at δ 6.17-6.40 [2].

Table II

Spectral Data of *N*-Methyl-4-pyridones and Thiopyridones

	IR (cm^{-1})		^1H NMR, δ [a] (deuteriochloroform)	
	C=S	C=O	H-5 (s)	N-CH_3 (s)
11a		1628	6.30	2.87
11b		1630	6.30	2.91
11d		1620	6.30	2.91
11e		1623	6.33	3.00
12a	1180			
12b	1175			
12c [b]	1170		6.53	3.42
12d [b]	1180		6.82	3.59
12e	1175		6.79	3.61
13e	1179			3.90
14d [c]	1172			3.77
14e [c]	1178			3.77
16a	1162			3.28
16b	1195			3.30
16d	1175			3.20
16e	1178			3.22

[a] s: Singlet. [b] Spectra carried out in deuterioacetone. [c] Spectra carried out in DMSO-d_6.

The reaction of 4*H*-pyran-4-ones with primary aliphatic amines leads to the formation of *N*-alkylpyridones [15]. Open chain diamino intermediates could be isolated in some cases [16]. The reaction of the 3-iodopyrones **3a,b, d,e** as well as the 3-iodothiopyrones **4a-e** with aqueous methylamine gave the corresponding *N*-methyl-3-iodopyridones **11a,b,d,e** and *N*-methyl-3-iodothiopyridones **12a-e**, respectively (Scheme I). The infrared spectra of the *N*-methylpyridones and thiopyridones showed the characteristic absorptions (Table II). As expected the H-5 proton in the ^1H nmr spectra of the *N*-methyl-3-iodothiopyridones resonated at lower field ($\Delta\delta$ 0.5 ppm) relative to their oxygen analogues (Table II).

Reaction of the 3-iodo-*N*-methylthiopyridone **12e** with bromine in acetic acid gave the respective 3-iodo-5-bromo-*N*-methylthiopyridone **13e**. With iodine monochloride, the 3-iodothiopyridones **12d,e** gave the 3,5-diiodo derivatives **14d,e**, which were also prepared from 2-aryl-6-phenyl-4*H*-pyran-4-thiones **15d,e** [17] and methylamine with subsequent reaction with iodine monochloride (Scheme I and Table II).

EXPERIMENTAL

Microanalyses were performed by the Microanalysis Unit, Cairo University, Cairo. Infrared spectra were measured with a Unicam, SP 1025 spectrophotometer for potassium bromide pellets. The ^1H nmr spectra were recorded on a Varian EM-390 90 MHz spectrometer with TMS as internal standard. Mass spectra were recorded on an AEI MS 30 spectrometer.

Table III

Analytical Data of the 3-Iodo-4*H*-pyran-4-ones and their Derivatives

	Mp °C	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	S% Calcd.	S% Found	Cl% Calcd.	Cl% Found	Br% Calcd.	Br% Found	I% Calcd.	I% Found
3a	170	$C_{17}H_{11}IO_2$	54.5	54.4	3.2	3.0									33.9	33.4
3b	185	$C_{18}H_{13}IO_2$	55.6	55.3	3.5	3.2									32.6	32.2
3c	192	$C_{18}H_{13}IO_3$	53.5	53.2	3.2	3.1									31.4	30.9
3d	197	$C_{17}H_{10}BrIO_2$	45.1	45.0	2.2	2.4							17.7	18.1	28.0	28.5
3e	196	$C_{17}H_{10}ClIO_2$	50.0	50.3	2.5	2.4					8.7	9.2			31.1	31.0
4a	220	$C_{17}H_{11}IOS$	52.3	52.2	2.8	2.7			8.2	8.0					32.6	32.8
4b	180	$C_{18}H_{13}IOS$	53.4	53.7	3.2	3.0			7.9	7.6					31.4	31.9
4c	230	$C_{18}H_{13}IO_2S$	51.4	51.3	3.1	3.4			7.6	7.3					30.2	29.7
4d	210	$C_{17}H_{10}BrIOS$	43.5	43.8	2.2	2.4			6.8	7.0			17.0	17.5	27.0	27.5
4e	186	$C_{17}H_{10}ClIOS$	48.1	48.3	2.4	2.6			7.5	7.8	8.3	8.8			29.9	29.7
9a	240	$C_{17}H_{12}INO_2$	52.4	52.2	3.1	3.1	3.6	3.8							32.7	32.9
9b	230	$C_{18}H_{14}INO_2$	53.6	53.3	3.5	3.8	3.5	3.8							31.5	31.0
9c	238	$C_{18}H_{14}INO_3$	51.6	51.4	3.3	3.3	3.3	3.0							30.3	30.8
9e	240	$C_{17}H_{11}ClINO_2$	48.2	48.0	2.6	2.4	3.3	3.0			8.4	8.9			30.0	30.5
10b	213	$C_{36}H_{32}N_6$	78.8	78.5	5.8	5.9	15.3	15.7								
10c	285	$C_{36}H_{32}N_6O_2$	74.5	74.3	5.5	5.5	14.5	14.8								
11a	180	$C_{18}H_{14}INO$	55.8	55.5	3.6	3.8	3.6	3.4							32.8	33.3
11b	160	$C_{19}H_{16}INO$	56.9	57.1	4.0	4.3	3.5	3.8							31.6	31.9
11d	170	$C_{18}H_{13}BrINO$	46.4	46.2	2.8	2.9	3.0	3.4					17.2	17.0	27.2	27.3
11e	200	$C_{18}H_{13}ClINO$	51.3	51.6	3.1	3.0	3.3	3.6			8.4	8.9			30.1	30.5
12a	240	$C_{18}H_{14}INS$	53.6	53.3	3.5	3.5	3.5	3.3	7.9	7.5					31.5	31.5
12b	250	$C_{19}H_{16}INS$	54.7	54.4	3.8	3.9	3.4	3.3	7.7	7.9					30.5	30.0
12c	262	$C_{19}H_{16}INOS$	52.7	52.8	3.7	3.5	3.2	3.3	7.8	8.1					29.3	29.9
12d	283	$C_{18}H_{13}BrINS$	44.8	44.9	2.7	2.8	2.9	2.8	6.6	6.3			16.6	16.8	26.4	26.5
12e	270	$C_{18}H_{13}ClINS$	49.4	49.3	3.0	3.0	3.2	3.1	7.3	7.5	8.1	8.5			29.0	29.2
13e	>300	$C_{18}H_{12}BrClINS$	41.8	41.5	2.3	2.2	2.7	2.5	6.2	6.1	6.9	6.5	15.5	15.4	24.6	24.3
14d	>300	$C_{18}H_{12}BrI_2NS$	35.5	35.3	2.0	2.0	2.3	2.0	5.3	5.0			13.2	13.7	41.8	41.5
14e	>300	$C_{18}H_{12}ClI_2NS$	38.3	38.3	2.1	2.1	2.5	2.2	5.7	5.9	6.3	5.9			45.1	45.5
16b	265	$C_{19}H_{17}NS$	78.4	78.3	5.8	5.8	4.8	4.5	11.0	10.7						
16d	283	$C_{18}H_{14}BrNS$	60.7	61.0	3.9	3.8	3.9	3.8	9.0	9.2			22.5	22.0		
16e	274	$C_{18}H_{14}ClNS$	69.3	69.3	4.5	4.5	4.5	4.3	10.3	10.0	11.4	11.0				

2-Aryl-3-iodo-6-phenyl 4*H*-pyran-4-ones **3** (Tables I, III).

A solution of iodine monochloride (0.4 g, 0.0025 mole) in dry chloroform (10 ml) was gradually added to a solution of the acetylenic β-diketone **1a-e** (0.5 g, 0.0020 mole) in dry chloroform (5 ml) with stirring for 30-60 minutes at room temperature. The precipitated 3-iodopyrone **3a-e** (80-87% yield) was filtered, washed with methanol, dried and crystallised from chloroform-methanol in pale yellow or colourless needles; ms: m/e (relative abundance) **3a**: M^+ 374 (100), 346 (36), 254 (4), 248 (11), 247 (52), 228 (28), 219 (8), 191 (20), 189 (5), 173 (10), 129 (7), 111 (5), 105 (90), 102 (20), 101 (14), 97 (8), 95 (8), 89 (10), 77 (65); **3c**: M^+ 404 (100), 376 (29), 278 (12), 277 (55), 254 (6), 250 (7), 249 (14), 239 (7), 228 (7), 221 (16), 204 (5), 203 (5), 188 (17), 178 (5), 135 (25), 133 (8), 132 (61), 128 (8), 127 (12), 125 (7), 117 (18), 111 (15), 109 (8), 105 (25), 101 (10), 97 (18), 95 (13), 92 (10), 89 (19), 85 (22), 77 (36).

The iodopyrones **3c,e** were recovered unchanged after refluxing their ethanolic solution with hydroxylamine hydrochloride and sodium acetate for five hours.

2-Aryl-3-iodo-6-phenyl-4*H*-pyran-4-thiones **4** (Tables I, III).

They were prepared from the respective 3-iodo-4*H*-pyran-4-ones **3** and phosphorus pentasulphide as described earlier [17].

2-Aryl-3-iodo-6-phenyl-4*H*-pyran-4-one Oximes **9** (Tables I, III).

They were prepared from the corresponding 3-iodo-4*H*-pyran-4-thiones **4** and hydroxylamine hydrochloride and sodium acetate in ethanol as described earlier [17].

Reaction of the 2-Aryl-3-iodo-6-phenyl-4*H*-pyran-4-ones with Hydrazine Hydrate.

A suspension of **3b,d,e** (0.4 g, 0.0010 mole) in ethanol (20 ml) was stirred with 99% hydrazine hydrate (1 ml, 0.0199 mole) at room temperature for 24 hours. The reaction mixture was then diluted with water, the respective 2-aryl-6-phenyl-4*H*-pyran-4-one [2,18] (70-74% yield) separated out.

Action of Hydrazine Hydrate on the 2-Aryl-3-iodo-6-phenyl-4*H*-pyran-4-thiones (Table III).

A solution of **4b,c** (0.4 g, 0.0005 mole) in ethanol (10 ml) was refluxed with hydrazine hydrate (1 ml, 0.0199 mole) for two hours. After concentration, the *N,N'*-di[1-phenyl-2-(3-arylpyrazol-5-yl)ethylidene]hydrazine **10b,c** (40-50% yield) that separated crystallised from methanol in yellow needles; **10b**: ν max (cm^{-1}): 1598 (C=N), 3213 (NH); ^1H nmr (DMSO-d_6): (δ/ppm) 2.26 (s, CH_3), 4.48 (s, CH_2), 6.17 (s, H-4), 7.55 (m, Ar-H), 12.85 (s,

NH); **10c**: ν max (cm^{-1}): 1605 (C=N), 3203 (NH); ^1H nmr (deuteriochloroform): (δ/ppm) 3.73 (s, OCH_3), 4.63 (s, CH_2), 6.40 (s, H-4), 7.77 (m, Ar-H).

N-Methyl-4-pyridones and Thiopyridones (Tables II, III).

A solution of the 3-iodopyrone **3a,b,d,e** or 3-iodothiopyrone **4a-e** or thiopyrone **15a,b,d,e** (0.5 g, 0.0013 mole) in ethanol (15 ml) and 33% aqueous methylamine solution (5 ml) was refluxed for 2-8 hours. The alcohol was evaporated under reduced pressure and the separated pyridone (60-85% yield) was crystallized from ethanol in yellow needles.

5-Bromo-2-(*p*-chlorophenyl)-3-iodo-1-methyl-6-phenyl-4-thiopyridone **13e** (Tables II, III).

To a solution of the 3-iodothiopyridone **12e** (0.4 g, 0.0010 mole) in glacial acetic acid (5 ml), bromine (0.2 g, 0.0012 mole) in glacial acetic acid (3 ml) was added drop by drop with stirring at room temperature. The precipitated product **13e** (95% yield), was crystallised from galcial acetic acid in pale yellow needles, mp >300°.

2-Aryl-3,5-diiodo-1-methyl-6-phenyl-4-thiopyridones **14** (Tables II, III).

To a solution of the 3-iodo-4-thiopyridone **12d,e** or 4-thiopyridone **16d,e** (0.4 g, 0.0010 mole) in chloroform (5 ml), iodine monochloride (0.2 g, 0.0012 mole) in chloroform (2 ml) was gradually added with stirring for one hour at room temperature and then the reaction mixture left overnight. The separated 3,5-diiodo-4-thiopyridone **14d,e** (50-60% yield) was crystallised from ethanol in brown needles.

REFERENCES AND NOTES

[1] I. G. Farbenind, A-G (Joachim Reitmann inventor), German Offen. 570,860 (1933).

[2] I. E. El-Kholy, M. G. Marei and M. M. Mishrikey, *J. Heterocyclic Chem.*, **16**, 737 (1979).

[3] H. C. Smitherman and L. N. Ferguson, *Tetrahedron*, **24**, 923 (1968).

[4] F. M. Dean, J. Goodchild, A. W. Hill, S. Murray and A. Zahman, *J. Chem. Soc., Perkin Trans. I*, 1335 (1975).

[5] H. Nakata and A. Tatematsu, *Tetrahedron Letters*, 4101 (1967).

[6] J. H. Bowie, R. G. Cooks, S.-O. Lawesson and C. Nolde, *J. Chem. Soc. B*, 616 (1967).

[7] S. Hannessian and J. S. Kaltenbronn, *J. Am. Chem. Soc.*, **88**, 4509 (1966).

[8] H. Budzikiewicz, J. I. Braumann and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).

[9] K. Heyns, R. Stute and H. Scharmann, *Tetrahedron*, **22**, 2223 (1966).

[10a] G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 4810 (1954); [b] I. E. El-Kholy, F. K. Rafla and G. Soliman, *J. Chem. Soc.*, 1857 (1962).

[11] F. Palazzo, *Gazz. Chim. Ital.*, **34**, I, 458 (1904); **36**, I, 59 (1906); I. E. El-Kholy, M. M. Mishrikey and M. G. Marei, *Egypt. J. Chem.*, accepted for publication (1983).

[12] C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.*, **76**, 3172 (1954).

[13] I. E. El-Kholy, M. M. Mishrikey and R. F. Atmeh, *J. Heterocyclic Chem.*, **11**, 487 (1974).

[14] C. Morin and R. Bengelmans, *Tetrahedron*, **33**, 3183 (1977).

[15] M. El-Kaschef and M. H. Nosseir, *J. Am. Chem. Soc.*, **82**, 4344 (1960).

[16] J. A. Van Allan, G. A. Reynolds, J. T. Alessi and S. Chany, *J. Heterocyclic Chem.*, **8**, 919 (1971).

[17] I. E. El-Kholy, F. K. Rafla and G. Soliman, *J. Chem. Soc.*, 2588 (1959).

[18] G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 1755 (1954).