

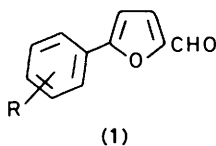
## Photochemical Synthesis of 3- and 5-Aryl-2-furyl Derivatives

Roberto Antonioletti, Maurizio D'Auria,\* Antonella De Mico, Giovanni Piancatelli,\* and Arrigo Scettri

Centro CNR per lo Studio della Chimica delle Sostanze Organiche Naturali c/o Dipartimento di Chimica, Università di Roma 'La Sapienza', P. le A. Moro 2, 00185 Roma, Italy

Irradiation of 3- and 5-bromofuran-2-carbaldehyde in aromatic solutions furnished, in good yield, 3- and 5-aryl-2-furyl derivatives. Analogously, 4,5-dibromofuran-2-carbaldehyde (**3**) and 4,5-dibromo-2-furyl methyl ketone (**5**) are useful starting materials for the synthesis of the previously unknown 5-aryl-4-bromo-2-furyl derivatives. Irradiation (in diethyl ether) of the above compounds furnished the debromination products in high yields. This method represents an efficient procedure for the synthesis of 4-bromofuran-2-carbaldehyde (**4**).

5-Arylfuran-2-carbaldehydes (**1**) are good starting materials for the synthesis of several compounds showing widespread biological activity, since some derivatives of (**1**) have been described with antibacterial,<sup>1-4</sup> antidepressant,<sup>5-7</sup> anti-inflammatory,<sup>8,9</sup> and spasmolytic<sup>10</sup> properties; furthermore, compounds of type (**1**) are useful as muscle relaxants<sup>11,12</sup> and for the treatment of asthma.<sup>13</sup>



The typical procedure for the preparation of compounds (**1**) involves the action of an aryldiazonium salt on 2-formylfuran. Unfortunately it suffers from some disadvantages, such as varying yields, formation of by-products, and poor utility for differently substituted furans. Furthermore, the introduction of the aryl group occurs only at the 5-position of the furan ring, so that only 5-aryl-2-furyl derivatives can be obtained. Therefore, the availability of a new and efficient route would be of great benefit.

In the course of our researches on the reactivity of furans and their usefulness as synthetic intermediates, we have found that, by irradiation with a high-pressure mercury arc lamp, 2-formyl- or 2-acyl-furans bearing a bromine atom at C-3 or C-5 undergo, in aromatic solvents, a photochemical substitution reaction leading to compounds of type (**1**) (Scheme).

The photochemical substitution of a halogen atom with aryl groups has been previously described for halogenobenzenes,<sup>14-16</sup> while no report is available in the furan field. All the experimental results on the photochemical behaviour of the starting materials (**2**)–(**6**) are collected in Table 1. Usually the reaction is carried out in benzene, *p*-xylene, and *m*-xylene solutions; it should be noted that in the latter case only the 2,4-xyllyl isomers (g.l.c.) are obtained. When other solvents, e.g. anisole and benzonitrile, are used, the reaction proceeds in a satisfactory manner yielding a *ca.* 1:1 mixture of two isomers† (g.l.c.), whose efficient isolation unfortunately could not be achieved. The photochemical replacement of bromine by aryl groups ceased at *ca.* 60–70% conversion, probably on account of competing u.v. absorption by the products. Also, since

arylfuran derivatives absorb at longer wavelength [*e.g.*, (**5**),  $\lambda_{\max}$ , 328 nm] than bromofurans [(**2**),  $\lambda_{\max}$ , 284 nm], the excitation of the latter is quenched by energy transfer to arylfurans. Furthermore, the photochemical process takes place with complete selectivity. As shown in Table 1, only bromine atoms either at C-3 or C-5 of the furan ring, conjugated with the carbonyl function, undergo substitution reaction with aryl groups, while the irradiation of the 4-bromo derivative (**4**) in benzene solution is quite ineffective. Therefore, this procedure proves to be particularly convenient for the synthesis of the hitherto unknown 5-aryl-4-bromo-2-furyl derivatives (**7a–g**) and **8a–c**) whose structures have been confirmed by <sup>13</sup>C n.m.r. spectral data (Table 2).

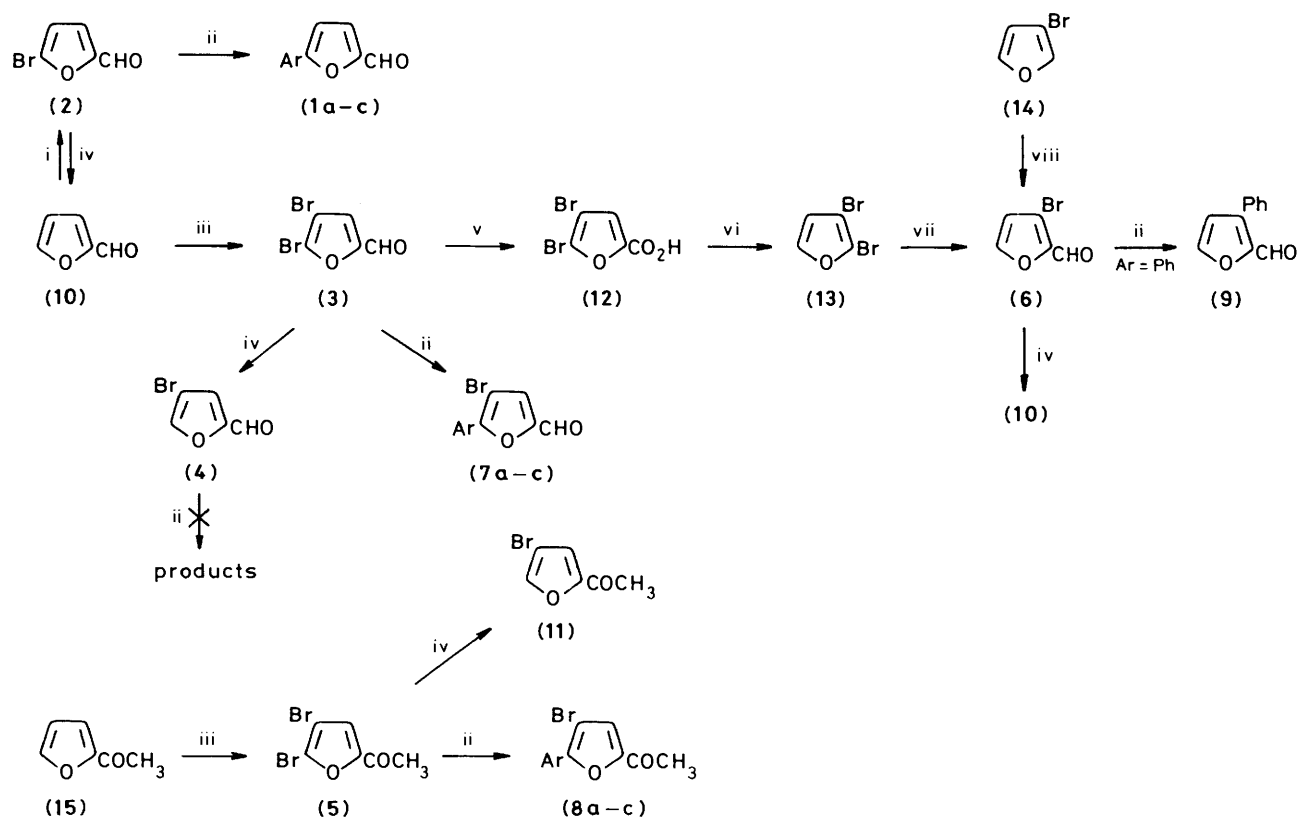
The greater reactivity of the halogen atoms at C-3 and C-5 is further shown by their selective and almost quantitative replacement by hydrogen atoms through the usual irradiation of compounds (**2**), (**3**), (**5**), and (**6**) in ethereal solution (Table 1). This method represents an effective procedure for the synthesis of 4-bromo-2-formylfuran (**4**) since the routes previously employed required treatment of the dibromide (**3**) with *o*-methoxyphenyl-lithium<sup>17</sup> or with zinc in ammonia.<sup>18</sup>

### Experimental

M.p.s were obtained with a Kofler block and are uncorrected. N.m.r. spectra were recorded with a Varian EM-360 spectrometer, using CCl<sub>4</sub> as solvent with tetramethylsilane as internal standard. <sup>13</sup>C N.m.r. spectra were recorded at 20 MHz with a Varian CFT-20 Fourier transform spectrometer, for CDCl<sub>3</sub> solutions. Chemical shifts are given in p.p.m. from internal Me<sub>4</sub>Si. I.r. spectra were obtained on Perkin-Elmer 257 and 457 spectrometers. Mass spectra were obtained on a AEI MS-12 instrument at 70 eV, by using direct insertion at a source temperature of 150 °C. U.v. spectra were recorded with a Varian DMS-90 spectrophotometer. Commercial Merck silica gel was used for column chromatography. Carlo Erba precoated silica gel plates were used in t.l.c.

For starting materials 5-bromofuran-2-carbaldehyde (**2**), 4,5-dibromofuran-2-carbaldehyde (**3**), 4-bromofuran-2-carbaldehyde (**4**), 4,5-dibromo-2-furyl methyl ketone (**5**), and 3-bromofuran-2-carbaldehyde (**6**) were used. Aldehyde (**2**) was prepared by reaction of furfural with bromine in 1,2-dichloroethane;<sup>19</sup> compounds (**3**) and (**5**) were synthesized by reaction of furfural and 2-furyl methyl ketone (**15**) respectively with bromine in the presence of AlCl<sub>3</sub>.<sup>20-25</sup> The 3-bromo aldehyde (**6**) can be prepared by reaction of 2,3-dibromofuran (**13**) [obtained from (**12**) by decarbonylation<sup>26</sup>] with Bu<sup>n</sup>Li and then with *N,N*-dimethylformamide (DMF),<sup>25,26</sup> or by reaction of 3-bromofuran (**14**) with lithium di-isopropylamide (LDA) and DMF.<sup>27</sup>

† Three positional isomers were expected when the substrate was irradiated in anisole or benzonitrile. However, only two g.l.c. peaks (capillary column) were observed, probably resulting from an *ortho*–*para* mixture.



**Scheme.** Reagents and conditions: i,  $\text{Br}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ; ii,  $h\nu$ ,  $\text{ArH}$ ; iii,  $\text{Br}_2$ ,  $\text{AlCl}_3$ ; iv,  $h\nu$ ,  $\text{Et}_2\text{O}$ ; v,  $\text{KMnO}_4$ ,  $\text{OH}^-$ ; vi,  $175^\circ\text{C}$ ,  $\text{Cu}$ , quinoline; vii,  $\text{BuLi}$ , DMF; viii, LDA, DMF

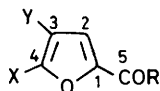
**Table 1.** Photochemical behaviour of furans (2)–(6)

Entry	Substrate					Solvent	Product	X	Y	Z	R	Yield (%)
		X	Y	Z	R							
1	(2)	Br	H	H	H	benzene	(1a)	phenyl	H	H	H	64
2	(2)	Br	H	H	H	<i>p</i> -xylene	(1b)	2,5-dimethylphenyl	H	H	H	60
3	(2)	Br	H	H	H	<i>m</i> -xylene	(1c)	2,4-dimethylphenyl	H	H	H	63
4	(2)	Br	H	H	H	$\text{Et}_2\text{O}$	(10)	H	H	H	H	100
5	(3)	Br	Br	H	H	benzene	(7a)	phenyl	Br	H	H	73
6	(3)	Br	Br	H	H	<i>p</i> -xylene	(7b)	2,5-dimethylphenyl	Br	H	H	75
7	(3)	Br	Br	H	H	<i>m</i> -xylene	(7c)	2,4-dimethylphenyl	Br	H	H	73
8	(3)	Br	Br	H	H	$\text{Et}_2\text{O}$	(4)	H	Br	H	H	96
9	(4)	H	Br	H	H	benzene	—	—	—	—	—	
10	(5)	Br	Br	H	$\text{CH}_3$	benzene	(8a)	phenyl	Br	H	$\text{CH}_3$	60
11	(5)	Br	Br	H	$\text{CH}_3$	<i>p</i> -xylene	(8b)	2,5-dimethylphenyl	Br	H	$\text{CH}_3$	63
12	(5)	Br	Br	H	$\text{CH}_3$	<i>m</i> -xylene	(8c)	2,4-dimethylphenyl	Br	H	$\text{CH}_3$	70
13	(5)	Br	Br	H	$\text{CH}_3$	$\text{Et}_2\text{O}$	(11)	H	Br	H	$\text{CH}_3$	82
14	(6)	H	H	Br	H	benzene	(9)	H	H	Phenyl	H	31
15	(6)	H	H	Br	H	$\text{Et}_2\text{O}$	(10)	H	H	H	H	92

**Photochemical Synthesis of Arylfuryl Derivatives.—General procedure.** The 2-furyl derivatives (2), (3), (5), and (6) (1 g) were each dissolved in an aromatic solvent (500 ml) and the solutions were outgassed with  $\text{N}_2$  for 1 h. Each mixture was then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a quartz water-jacket. After 2 h each mixture was dissolved in  $\text{Et}_2\text{O}$  and washed with brine. The neutral ethereal phase was dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent yielded a crude

product which was chromatographed on  $\text{SiO}_2$ . Elution with  $\text{CHCl}_3$ -*n*-hexane (3:2) gave the pure products (Table 1). The following arylfuryl derivatives were thus prepared.

5-Phenylfuran-2-carbaldehyde (1a). Viscous oil<sup>30</sup> (Found: C, 76.8; H, 4.6. Calc. for  $\text{C}_{11}\text{H}_8\text{O}_2$ : C, 76.73; H, 4.68%);  $\delta_{\text{H}}$  9.42 (1 H, s), 7.60 (2 H, m), 7.17 (3 H, m), 7.06 (1 H, d,  $J$  4 Hz), and 6.62 (1 H, d,  $J$  4 Hz);  $\nu_{\text{max}}$  1 679, 1 675, 1 569, 1 523, 1 475, 1 451, 1 392, 1 256, 1 029, 968, 920, 762, and 690  $\text{cm}^{-1}$ ;  $m/z$  172 (100%), 171 (31), and 115 (53).

Table 2. <sup>13</sup>C N.m.r. data of some furans

Substrate	C-1 <sup>a</sup>	C-2 <sup>a</sup>	C-3 <sup>a</sup>	C-4 <sup>a</sup>	C-5 <sup>a</sup>	R <sup>a</sup>
(10) <sup>b</sup>	153.8(s)	121.6(d)	112.9(d)	148.7(d)	178.2(d)	—
(2)	154.5(s)	123.0(d)	122.2(d)	130.9(s)	176.3(d)	—
(1a)	159.5(s)	123.3(d)	107.7(d)	152.2(s)	177.2(d)	—
(1b)	159.7(s)	122.9(d)	110.9(d)	151.7(s)	177.3(d)	—
(3)	153.7(s)	123.4(d)	105.0(s)	131.3(s)	176.0(d)	—
(7a)	153.9(s)	125.7(d)	98.2(s)	150.5(s)	176.9(d)	—
(5)	153.8(s)	120.4(d)	104.5(s)	128.6(s)	184.6(s)	25.5(q)
(8a)	150.6(s)	122.3(d)	98.0(s)	148.1(s)	185.8(s)	25.8(q)

<sup>a</sup> Multiplicity in off-resonance decoupled spectrum: s = singlet, d = doublet, t = triplet, q = quartet. <sup>b</sup> E. Breitmaier, G. Haas, and W. Voelter, 'Atlas of Carbon-13 NMR Data,' Heyden, London, 1979.

5-(2,5-Dimethylphenyl)furan-2-carbaldehyde (1b). Viscous oil (Found: C, 78.0; H, 6.1. C<sub>13</sub>H<sub>12</sub>O<sub>2</sub> requires C, 77.98; H, 6.04%); δ<sub>H</sub> 9.43 (1 H, s), 7.36 (1 H, s), 7.05 (1 H, d, J 4 Hz), 6.90 (2 H, s), 6.50 (1 H, d, J 4 Hz), 2.41 (3 H, s), and 2.30 (3 H, s); ν<sub>max</sub> 1 680, 1 675, 1 575, 1 515, 1 502, 1 480, 1 462, 1 400, 1 381, 1 352, 1 288, 1 257, 1 146, 1 035, 975, 790, and 770 cm<sup>-1</sup>; m/z 200 (100%), 143 (46), 141 (14), 128 (35), and 115 (14).

5-(2,4-Dimethylphenyl)furan-2-carbaldehyde (1c). Viscous oil (Found: C, 78.0; H, 6.0%); δ<sub>H</sub> 9.40 (1 H, s), 7.44 (1 H, d, J 8 Hz), 7.06 (1 H, d, J 4 Hz), 6.84 (1 H, d, J 8 Hz), 6.80 (1 H, s), 6.43 (1 H, d, J 4 Hz), 2.40 (3 H, s), and 2.26 (3 H, s); ν<sub>max</sub> 1 680, 1 672, 1 616, 1 518, 1 470, 1 385, 1 352, 1 283, 1 244, 1 031, 973, 790, and 770 cm<sup>-1</sup>; m/z 200 (100%), 143 (50), 141 (11), 129 (11), and 128 (30).

4-Bromo-5-phenylfuran-2-carbaldehyde (7a). Viscous oil (Found: C, 52.7; H, 2.8. C<sub>11</sub>H<sub>7</sub>BrO<sub>2</sub> requires C, 52.61; H, 2.79%); δ<sub>H</sub> 9.55 (1 H, s), 8.00 (2 H, m), 7.32 (3 H, m), and 7.18 (1 H, s); ν<sub>max</sub> 1 690, 1 517, 1 478, 1 445, 1 351, 1 282, 1 135, 1 082, 956, 687, and 672 cm<sup>-1</sup>; m/z 252 (99%), 250 (100), 210 (30), 208 (23), 195 (42), 193 (44), 119 (18), 117 (20), 115 (30), 114 (48), and 113 (17).

4-Bromo-5-(2,5-dimethylphenyl)furan-2-carbaldehyde (7b). Viscous oil (Found: C, 56.0; H, 4.0. C<sub>13</sub>H<sub>11</sub>BrO<sub>2</sub> requires C, 55.93; H, 3.94%); δ<sub>H</sub> 9.52 (1 H, s), 7.23 (2 H, s), 7.10 (2 H, m), and 2.31 (6 H, s); ν<sub>max</sub> 1 690, 1 522, 1 474, 1 340, 1 278, 1 210, and 1 120 cm<sup>-1</sup>; m/z 280 (100%), 278 (98), 223 (23), 221 (25), 199 (23), 171 (18), 170 (23), 143 (38), 142 (64), 141 (55), 128 (27), and 115 (37).

4-Bromo-5-(2,4-dimethylphenyl)furan-2-carbaldehyde (7c). Viscous oil (Found: C, 56.0; H, 3.9%); δ<sub>H</sub> 9.50 (1 H, s), 7.34 (1 H, d, J 9 Hz), 7.22 (1 H, s), 6.97 (1 H, d, J 9 Hz), 7.01 (1 H, s), and 2.28 (6 H, s); ν<sub>max</sub> 1 692, 1 620, 1 522, 1 474, 1 380, 1 345, 1 283, 1 230, 1 122, and 961 cm<sup>-1</sup>; m/z 280 (97%), 278 (100), 223 (27), 221 (28), 205 (12), 199 (12), 171 (27), 170 (26), 143 (36), 142 (54), 141 (60), 128 (23), 119 (25), 117 (27), and 115 (34).

4-Bromo-5-phenyl-2-furyl Methyl Ketone (8a). Viscous oil (Found: C, 54.4; H, 3.4. C<sub>12</sub>H<sub>9</sub>BrO<sub>2</sub> requires C, 54.36; H, 3.40%); δ<sub>H</sub> 7.86 (2 H, m), 7.25 (3 H, m), 7.03 (1 H, s), and 2.36 (3 H, s); ν<sub>max</sub> 1 686, 1 518, 1 480, 1 447, 1 364, 1 298, 1 272, 1 163, 953, and 924 cm<sup>-1</sup>; m/z 266 (100%), 264 (100), 251 (86), 195 (51), 193 (51), 114 (86), 88 (21), and 77 (25).

4-Bromo-5-(2,5-dimethylphenyl)-2-furyl Methyl Ketone (8b). Viscous oil (Found: C, 57.3; H, 4.4. C<sub>14</sub>H<sub>13</sub>BrO<sub>2</sub> requires C, 57.36; H, 4.44%); δ<sub>H</sub> 7.20 (1 H, s), 7.11 (1 H, s), 7.03 (2 H, m), 2.40 (3 H, s), and 2.33 (3 H, s); ν<sub>max</sub> 1 688, 1 520, 1 480, 1 360, 1 298, 1 272, 1 159, 964, and 924 cm<sup>-1</sup>; m/z 294 (97%), 292 (100), 279 (29), 277 (31), 223 (42), 221 (42), 213 (28), 170 (36), 142 (80), 141 (90), 115 (53), and 77 (20).

4-Bromo-5-(2,4-dimethylphenyl)-2-furyl Methyl Ketone (8c). Viscous oil (Found: C, 57.3; H, 4.45%); δ<sub>H</sub> 7.27 (1 H, d, J 9 Hz),

7.08 (1 H, s), 6.90 (1 H, d, J 9 Hz), 6.89 (1 H, s), 2.37 (3 H, s), and 2.32 (3 H, s); ν<sub>max</sub> 1 688, 1 617, 1 522, 1 477, 1 362, 1 298, 1 273, 1 157, and 960 cm<sup>-1</sup>; m/z 294 (100%), 292 (100), 279 (29), 277 (29), 223 (52), 221 (52), 213 (18), 185 (22), 170 (47), 142 (67), 141 (94), and 116 (51).

3-Phenylfuran-2-carbaldehyde (9). Viscous oil (Found: C, 76.7; H, 4.6. C<sub>11</sub>H<sub>8</sub>O<sub>2</sub> requires C, 76.73; H, 4.68%); δ<sub>H</sub> 9.60 (1 H, s), 7.1—7.7 (6 H, m), and 6.58 (1 H, d, J 2 Hz); ν<sub>max</sub> 1 685, 1 502, 1 472, 1 450, 1 414, 1 372, 1 368, 1 260, and 1 158 cm<sup>-1</sup>; m/z 172 (89%), 171 (100), 115 (62), and 89 (15).

**Photochemical Debromination.—General procedure.** The 2-furyl derivatives (2), (3), (5), and (6) (2.5 g) were each dissolved in Et<sub>2</sub>O (500 ml) and the solutions were outgassed with N<sub>2</sub> for 1 h. Each mixture was irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios Italquartz) surrounded by a quartz water-jacket. After 1 h the mixtures were each washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent yielded a crude product which was chromatographed on SiO<sub>2</sub>. Elution with CHCl<sub>3</sub>-n-hexane (3:2) gave the pure products (Table 1). The following products were thus prepared.

4-Bromofuran-2-carbaldehyde (4), m.p. 51—52 °C (lit.,<sup>28</sup> 52 °C).

4-Bromo-2-furyl methyl ketone (11), m.p. 69—70 °C (lit.,<sup>29</sup> 69.5—70.5 °C).

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