AN IMPROVED SYNTHETIC METHOD FOR 5-ARYL-2-FURANCARBALDEHYDE

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Abstract – An improved synthetic method for the preparation of 5-aryl-2-furancarbaldehyde via a photochemical arylation of 5-iodo-2-furancarbaldehyde is described.

In our recent paper[1] we have described a new synthetic method for the preparation of 3- and 5-aryl-2-furancarbaldehydes 2 from the corresponding 3- and 5-bromofuran derivatives 1 by a photochemical reaction in aromatic medium.
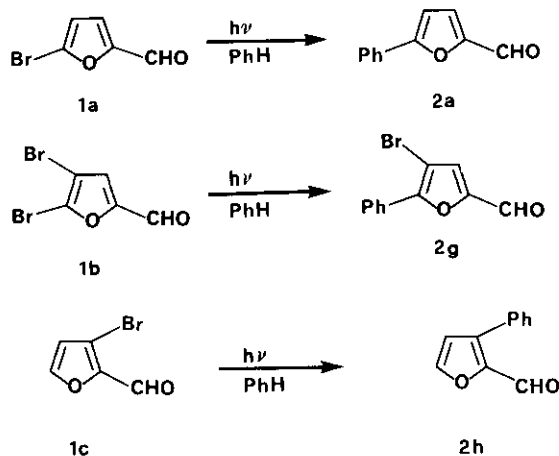
In particular, 5-aryl-2-furancarbaldehydes have been considered important building blocks in the synthesis of several compounds with antibacterial[2], antidepressant[3], antiinflammatory[4], and spasmolytic[5] properties. However our procedure, showing a progress in comparison with the previous synthetic method (reaction of an aryldiazonium salt on furancarbaldehyde), suffers from some disadvantages. In particular, we obtain only 60 - 65% conversion yields, and, furthermore, we can use it only with liquid, low-boiling aromatic substrates. In this paper we want to present the solution to this problem, allowing a general synthetic method for the synthesis of 2. Recently we have reported[6] that the mechanism of the conversion 1 → 2 probably involves the formation of the exciplex 3 in the triplet state.

$$\left[\quad \underset{O}{\overset{R}{\bigcirc}} \quad PhH \overset{+}{\cdot} \right] \qquad \underline{3}$$
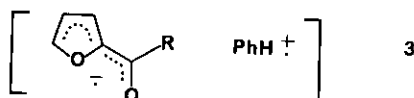
The formation of an exciplex followes the Weller equation (1)[7], where $E_{\frac{1}{2}}^{Ox}(D)$ is the oxidation potential of the donor, $E_{\frac{1}{2}}^{Red}(A)$ the reduction potential of the acceptor, ΔE_{exc} the excitation energy, $F = 96490$ C, $e = 1.602 \times 10^{-19}$ C, $\varepsilon_0 = 8.854 \times 10^{-12}$ Fm^{-1}, ε is the dielectric constant of the solvent, and a is the encounter distance 7 Å.

$$\Delta G = F \left(E_{\frac{1}{2}}^{Ox}(D) - E_{\frac{1}{2}}^{Red}(A) \right) - \Delta E_{exc} + \frac{e^2 N}{4\pi\varepsilon_0 a} \left(\frac{1}{\varepsilon} - \frac{2}{37.5} \right) \qquad (1)$$

On the basis of this equation we can predict that a) the conversion $\underline{1} \rightarrow \underline{2}$ is favoured in polar solvents that minimize the last term of the eq. 1, and b) we can improve the reactivity of the substrate selecting a compound with a lower $E_{\frac{1}{2}}^{Red}(A)$. We have tested this hypothesis. When the solvent is acetonitrile ($\varepsilon = 37.5$) the eq. 1 can be simplified to the eq. 2.

$$\Delta G \text{ (eV)} = E_{\frac{1}{2}}^{Ox}(D) - E_{\frac{1}{2}}^{Red}(A) - \Delta E_{exc} - 0.06 \qquad (2)$$

$E_{\frac{1}{2}}^{Red}$ values (5-bromofurancarbaldehyde $= -1.48$ V; 5-iodofurancarbaldehyde $= -0.94$ V, Fig. 1) were calculated on the basis of polarographic spectra obtained in MeOH (10^{-3} M) in presence of tetrabutyl ammonium iodide (Fig. 1). ΔE_{exc} (3.75 eV) is the energy of the triplet state calculated on the basis of the phosphorescence spectrum of 5-bromo-2-furancarbaldehyde[6]. This value can be considered constant: in fact we have not observed any difference in the phosphorescence emission between 5-bromofurancarbaldehyde and the parent compound furancarbaldehyde[8]. This way, in presence of benzene ($E_{\frac{1}{2}}^{Ox} = 2.11$ V[7]) we obtain $\Delta G = -0.22$ eV for 5-bromofurancarbaldehyde and $\Delta G = -0.76$ eV for 5-iodofurancarbaldehyde.

The comparison of these data allows us to conclude that the conversion $\underline{1} \rightarrow \underline{2}$ is favoured in acetonitrile and that we have to expect a greater reactivity of 5-iodofuran derivative than $\underline{1a}$.

In a typical experimental procedure, 5-iodo-2-furancarbaldehyde[9] (2 g) is dissolved in acetonitrile (250 ml); then the aromatic substrate (15 g) is added and the solution is outgassed with N_2 for 1 h. The mixture is then irradiated in an immersion apparatus with a 500 W high pressure mercury arc surrounded by a quartz water jacket. Afer 4 h the mixture is extracted with diethyl ether and washed with 0.1 N sodium thiosulfate solution and then with brine. The neutral ethereal phase
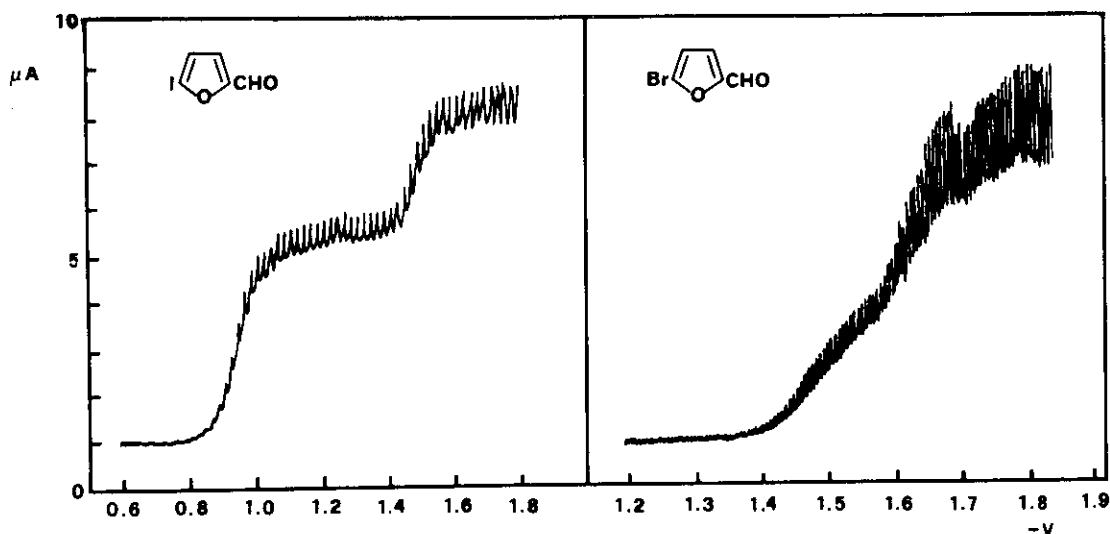
Fig. 1 – Polarographic waves of 5-iodo-2-furaldehyde and 5-bromo-2-furaldehyde

is dried over Na_2SO_4. Removal of the solvent yields a crude product which is chromatographed on SiO_2. Elution with $CHCl_3$ – n-hexane (3:2) gives the pure products[10] (Table). The positional isomers (entries 2 and 5) can be separated by column chromatography with a Lobar LiChroprep Si-60 eluting with CCl_4 – n-hexane (1:1).

Table

Entry	ArH	Product	Ar	Yield(%)[a]
1	Benzene	2a	Phenyl	91
2	Chlorobenzene	2b	2-Chlorophenyl	55[b]
3	Naphthalene	2c	2-Naphthyl	83
4	p-Xylene	2d	2,5-Dimethylphenyl	78
5	Anisole	2e	2-Methoxyphenyl	60[c]
		2f	4-Methoxyphenyl	19[c]

a) All yields refer to isolated chromatographically pure products. b) We obtain also an unresolved 1:1 mixture (30 % yield) of meta – para compounds. c) We obtain also 7% of meta compound.

We have to show both the high yields of the conversion and the simplicity of the

procedure. The only limitation is the formation of positional isomers when we use monosubstituted aromatic substrates. However, we have to note that we obtain mainly the ortho compound, while we can expect a mixture of three positional isomers.

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10) 2a: NMR (CCl_4, δ): 9.42 (s, 1 H), 7.60 (m, 2 H), 7.17 (m, 3 H), 7.06 (d, 1 H, J = 4 Hz), 6.62 (d, 1 H, J = 4 Hz). IR (CCl_4): 1679, 1675, 1569, 1523, 1475, 1451, 1329, 1256, 1029, 968, 920, 762, 690 cm^{-1}. MS (m/z): 172 (M^+). 2b: NMR ($CDCl_3$, δ): 9.58 (s, 1 H), 7.92 (m, 1 H), 7.3 (m, 3 H), 7.22 (s, 2 H). IR (CS_2): 1688, 756. MS (m/z): 206 (M^+). 2c: NMR (CCl_4, δ): 9.55 (s, 1 H), 8.14 (m, 1 H), 7.7 (m, 1 H), 7.62 (m, 2 H), 7.42 (s, 1 H), 7.32 (m, 2 H), 7.15 (d, 1 H, J = 4 Hz), 6.68 (d, 1 H, J = 4 Hz). IR (film): 1680, 1568, 1520, 1502, 1458, 1452, 1390, 1332, 1270, 1240, 1218, 1190, 1165, 1127, 1028, 1001, 970, 917, 863, 800, 770, 760 cm^{-1}. MS (m/z): 226 (M^+). 2d: NMR (CCl_4, δ): 9.43 (s, 1 H), 7.36 (s, 1 H), 7.05 (d, 1 H, J = 4 Hz), 6.90 (s, 2 H), 6.50 (d, 1 H, J = 4 Hz), 2.41 (s, 3 H), 2.30 (s, 3 H). IR (CCl_4): 1680, 1675, 1575, 1515, 1502, 1480, 1462, 1400, 1381, 1352, 1288, 1257, 1146, 1035, 975, 790, 770 cm^{-1}. MS (m/z): 200 (M^+). 2e: NMR (CCl_4, δ): 9.50 (s, 1 H), 7.9 (m, 1 H), 7.2 - 7.0 (m, 2 H), 7.10 (d, 1 H, J = 4 Hz), 6.93 (d, 1 H, J = 4 Hz), 6.90 (m, 1 H), 3.90 (s, 3 H). IR (CS_2): 1682, 1120, 1028, 750 cm^{-1}. MS (m/z): 202 (M^+). 2f: NMR (CCl_4, δ): 9.49 (s, 1 H), 7.58 (d, 2 H, J = 8 Hz), 7.10 (d, 1 H, J = 4 Hz), 6.78 (d, 2 H, J = 8 Hz), 6.55 (d, 1 H, J = 4 Hz), 3.75 (s, 3 H). IR (CS_2): 1680, 1256, 1175, 1027, 830, 785, 765, 752 cm^{-1}. MS (m/z): 202 (M^+).