HETEROCYCLES, Vol. 29, No. 4, 1989

MONOFUNCTIONALIZATION STUDY OF FURAN-2,5-DICARBOXALDEHYDE. CONFORMATIONAL ANALYSIS AND MODEL REACTIONS

Irmina Hernández-Fuentes*, Cristina Abradelo, Carmen Domínguez, and Aurelio G. Csákÿ
Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain

Joaquín Plumet*
Facultad de Ciencias, Universidad de Extremadura, 06071 Badajoz, Spain

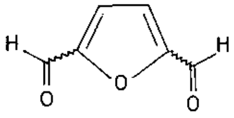
Carlos Cativiela and José Antonio Mayoral
Facultad de Ciencias, Instituto de Ciencias de los Materiales de Aragón, 50009 Zaragoza, Spain

Antoine Gaset and Luc Rigal
Ecole Superieure de Chimie, Institut Nationale Polytechnique, 31077 Toulouse Cedex, France

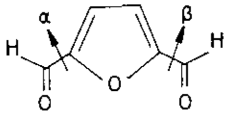
Abstract- The possible monofunctionalization of furan-2,5-dicarboxaldehyde is verified by means of several model reactions. On the other hand conformational analysis of FDC is analized by a combined experimental dipole moment determination-theoretical MNDO calculation.

Furan-2,5-dicarboxaldehyde, FDC, is an important synthetic intermediate isolated from the biomass[1] and useful for the preparation of a variety of compounds of industrial and farmacological interest[2]. It is also a widely used starting material both in bridged annulene and crown ether chemistry[3]. Largely, the reactions of FDC imply the functionalization of both formyl groups[4,5]. Thus, direct monofunctionalization of FDC appears to be desirable in order to improve the synthetic versatility of this compound.

Direct functionalization of one carbonyl group in FDC has been performed for the following reactions: i) reaction of 1 with MeOH/TsOH afforded the monoacetal 5[12]; ii) reaction with acetone yielded 6[13]; iii) other aldolic condensations with aromatic ketones gave products 7 and 8 depending on the reaction conditions (Table 1)

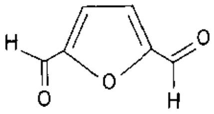


1



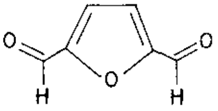
2

α = β = 0°



3

α=180°, β=0°



4

α = β = 180°

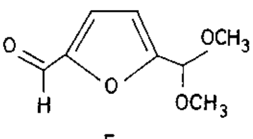
Table 1

Aldolic condensations of FDC with aromatic ketones

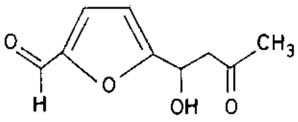
	Conditions				Yield(%)[a]	
Ar-	Base	Solvent	FDC/RCOAr	time	7	8
Phenyl	NaOH,10%	EtOH	1:1	40 min	14	73
2-Thienyl	NaOH,10%	EtOH	1:1	40 min	16	42
p-Methoxyphenyl	NaOH,10%	EtOH	1:1	40 min	25	--
p-Nitrophenyl	NaOH,10%	EtOH	1:1	40 min	--	--
2-Furyl	NaOH,10%	EtOH	1:1	40 min	30	36
p-Methoxyphenyl	NaOH,1%	EtOH/H_2O	1:1	2 days	10	--
p-Methoxyphenyl	NaOH,1%	EtOH/H_2O	1:1.5	7 days	12	--
p-Methoxyphenyl	NaOH,1%	EtOH/H_2O	1:2	3 days	18	--
p-Methoxyphenyl	NaOH,1%	EtOH/H_2O	1:4	2 days	60	--
Phenyl	NaOH,1%	EtOH/H_2O	1:1	4 days	41	49
2-Furyl	NaOH,1%	EtOH/H_2O	1:1	2 days	--	--
2-Thienyl	NaOH,1%	EtOH/H_2O	1:1	4 days	32	30
p-Nitrophenyl	NaOH,1%	EtOH/H_2O	1:1	1 day	17	48

a) In pure, isolated product. See reference 14.

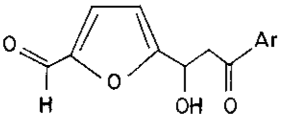
On the other hand, the conformational equivalence of both formyl groups has been evaluated in the following way: For 1 there are three a priori more stable conformations with both formyl groups coplanar with the furan ring: 2, ZZ; 3, EZ, and 4, EE.



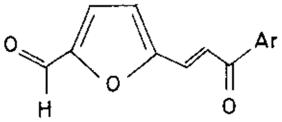
5



6



7



8

SCF-MNDO[6] calculations show populations of 7.1% for 2, 62% for 3 and 30.9% for 4 obtained from the theoretical heats of formation of the three coplanar[7] conformations. The calculated dipole moment is μ= 2.57 D. The experimental dipole moment[8] (μ = 3.16 D in benzene and in cyclohexane) is in reasonably good agreement with the theoretical one[9]. This indicates that in FDC there is a conformational equilibrium where the EZ conformation 3 has the biggest contribution[10,11].

In conclusion, conformational analysis of FDC indicates no equivalence of both aldehyde groups. Experimental comprobation has been performed for two model reactions: monoprotection with MeOH/TsOH and aldolic condensations. Other reactions and synthetic utility of monofunctionalized FDC are being currently explored in our laboratories.

ACKNOWLEDGEMENTS

This research was in part sponsored by the CICYT (Ministerio de Educación y Ciencia, Spain). Grants No. 320/84 and 2953/83. Two of us (C.D. and A.G.C.) thank the Comunidad Autónoma de Madrid (Consejería de Educación) for a grant.

REFERENCES AND NOTES

1. See, for example, A.Gaset, L.Rigal, G.Paillasa, and J.R.Salome, French Patent 83.14.646 (1983) (C.A., 215715 (1985)).
2. See, for example:
    - a) A.D.Voitenko, J.Kastrons, K.V.Medne, and S.Hillers, Khim.Farm.Zh., 1972, 6, 24.
    - b) Z.Moulongui, M.Delmas, and A.Gaset, Synth.Comm., 1984, 14, 701.
    - c) K.Y.Novitskii, V.P.Volkov, and Y.K.Yur'ev, Zh.Obshchei Khim., 1962, 32, 399.
3. See, for example:
    - a) T.M.Cresp and M.V.Sargent, J.Chem.Soc., Perkin Trans. I, 1972, 2961.
    - b) A.Strand, B.Thulin, and O.Wennestron, Acta Chem.Scand. B, 1977, 31, 1977.
    - c) D.K.Cook and D.E.Fenton, J.Chem.Soc., Dalton Trans., 1979, 810.
    - d) B.Thulin, O.Wennestron, I.Somfai, and B.Chmielarz, Acta Chem.Scand. B, 1977, 31, 135.
    - e) H.Ogawa, C.Fukuda, T.Imoto, I.Miyamoto, H.Kato, and Y.Taniguchi, Angew.Chem., 1983, 95, 412.
    - f) H.Ogawa, C.Fukuda, T. Imoto, I.Miyamoto, H.Kato, and Y.Taniguchi, Tetrahedron Lett., 1983, 24, 1045.
    - g) S.M.Nelson, F.S.Esmo, and M.G.B.Drew, J.Chem.Soc., Dalton Trans., 1983, 1857.
    - h) S.M.Nelson, F.S.Esmo, and M.G.B.Drew, J.Chem.Soc., Chem.Commun., 1981, 388.
4. To the best of our knowledge only a few cases of direct monofuctionalization of FDC have been published. See, for example:
    - a) H.Saikachi, H.Ogawa, Y.Minami, and K.Sato, Chem.Pharm.Bull, 1970, 18, 465.
    - b) C.Domínguez, G.Escobar, J.Plumet, A.Gaset, and L.Rigal, An.Quim., 1986, 82C, 241.
    - c) R.G.Johnston and D.Kidd, J.Chem.Soc., 1964, 4730.
5. Several cases of monofunctionalization of FDC via protection-deprotection of one aldehyde group have been reported. See, for example:
    - a) T.M.Cresp, M.V.Sargent, and P.Vogel, J.Chem.Soc., Perkin Trans. I, 1974, 37.
    - b) B.L.Feringa, R.Hulst, R.Rikers, and L.Brandsma, Synthesis, 1988, 316.
6. M.J.S.Dewar and W.Thiel, J.Am.Chem.Soc., 1977, 99, 4899.
7. Two energetic maxima have been obtained corresponding to the conformations $\alpha = \beta = 90^{\circ}$ and $\alpha = 270^{\circ}$ and $\beta = 90^{\circ}$. Three minima are present corresponding to the coplanar position of the aldehyde group. The energetic barrier to the interconversion planar-non planar conformations have been

stimated in, at least, 2.75 Kcal/mol.

8. Determined in benzene and in cyclohexane solutions at concentrations between $1.10^{-3} < \omega_2 < 5.5.10^{-3}$ for benzene solutions and $2.10^{-4} < \omega_2 < 9.10^{-4}$ for cyclohexane ones, expressed as solute weight fraction, using the Debye method, by application of Halverstadt and Kumler and Guggenheim-Smith equations. Full experimental details including molar polarization and molar refraction of solute at infinite dilution, and dependences of dielectric constants (ε), refractive index (n), and dependence of specific volume (v) with concentrations ranging will be published elsewhere and be done upon request. Correspondence to Prof. I.Hernández-Fuentes. For the method applied, see P.Debye, Phys.Z., 1912, 13, 97; J.F.Halverstadt and D.W.Kumler, J.Am.Chem.Soc., 1942, 64, 2988; E.Guggenheim, Trans.Faraday Soc., 1949, 95, 714; ibid., 1951, 47, 573; J.W.Smith, Ibid., 1950, 46, 394

9. Solvent effects on the conformational equilibrium would be negligible in the conditions of "infinite dilutions" (see reference 8), although the solvent appears to play an important role in conformational equilibrium of furfural itself. See:

   a) F.Mouning, H.Dreizler, and H.D.Rudolph, Z.Naturforsch., 1965, 203, 1323

   b) K.Dahlquist and S.Forsen, J.Chem.Phys., 1965, 69, 4062

   c) R.J.Abraham and T.M.Siverns, Tetrahedron, 1972, 28, 3015

   d) F.A.Miller, W.G.Fateley, and R.E.Withkowsky, Spectrochimica Acta, 1967, 23a, 891.

   See also A.L.Mc.Clellan, "Tables of Experimental Dipole Moments", Freeman, London, 1963.

10. To the best of our knowledge no data are reported concerning to the conformational preferences of FDC. See however T.N.Huckerby, Tetrahedron Lett., 1971, 3497.

11. Comparison of experimental and theoretical dipole moments constitutes a useful tool in conformational analysis. For recent examples see:

    a) O.Arjona, J.Plumet, M.D.K.Sabbagh, I.Hernández-Fuentes, C.Abradelo, M.J.García-Santos, C.Cativiela, and J.A.Mayoral, J.Chem.Research, 1988, 128.

    b) M.Moreno-Mañas, A.González, C.Jaime, J.Marquet, I.Hernández-Fuentes, C.Salom, and J.Bellanato, J.Chem.Soc., Chem.Commun., 1987, 1706.

12. From 124 mg FDC (1 mmol) in anhydrous methanol (15 ml) with a trace amount of p-toluenesulphonic acid at reflux during 18 h. Yield 73%. Ir (CCl_4) 2829, 1680, 1580, 1520 cm^{-1}. ^1H-Nmr (60 MHz, $CDCl_3$) 3.4 (s, 6H, OMe); 5.4 (s, 1H, CH); 7.1,

6.6 (AB_q, 2H, J=4Hz, H_{furan}); 9.56(s, 1H, $H_{aldehyde}$).

13. From 248 mg FDC (2 mmol) in 10 ml of a mixture EtOH:H_2O (1:1), 1.17 g of acetone (20 mmol) and eight drops of 1% NaOH, at 0°C. Reaction time, 1h. Yield 65%, bp 200°C (0.1 mmHg). Ir (CCl_4) 3400, 2840, 2920, 1670, 1710 cm^{-1}. ^1H-Nmr (60 MHz, $CDCl_3$) 2.23 (s, 3H, H-C(9)); 3.0 (d, 2H, J=6Hz, H-C(7)); 4.0 (s, broad, 1H, O<u>H</u>); 5.2 (t, 1H, J=6Hz, H-C(6)); 6.5 (d, 1H, J=4Hz, H-C(4)); 7.2 (d, 1H, J=4 Hz, H-C(3)); 9.5 (s, 1H, H-C(1)). ^{13}C-Nmr (80 MHz, $CDCl_3$) 207 (C(8)); 177 (C(1)); 162 (C(2)); 152 (C(5)); 123 (C(3)); 109 (C(4)); 63 (C(6)); 48 (C(7)); 30 (C(9)).

    Reaction of FDC with acetone did not afford the expected aldol. In the presence of a reducting medium (H_2-$BaSO_4$) the reduced product may be isolated. See ref 2c and:

    a) G.Drechler and G.Kopperschläger, J.Prakt.Chem., 1965, 27, 258.

    b) J.H.Poirier and G.Dujardin, Heterocycles, 1987, 25, 399.

14. All reactions were performed at 0°C. Products 7 and 8 have been separated by silica gel column chromagography employing a mixture of n-hexane/ethyl acetate (1:2). Spectroscopic and analytical data are in good agreement with the proposed structures. Full details will be published elsewhere and may be done upon request. Correspondence to Prof.J.Plumet.

Received, 8th December, 1988