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DIRECT CYANATION OF THE FURAN NUCLEUS BY CHLOROSULPHONYL ISOCYANATE

ARTHUR J. FLOYD*, RICHARD G. KINSMAN, YUSUF ROSHAN-ALI AND DAVID W. BROWN.

School of Chemistry, University of Bath, Bath, Avon. BA2 7AY

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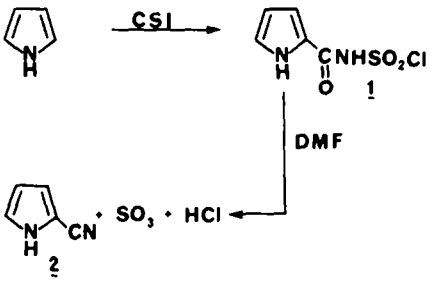
Abstract - A series of furans are converted directly, by reaction with chlorosulphonyl isocyanate, into furancarbonitriles. A route to furfuralcarbonitriles is described involving a new application of the ruthenium dioxide - sodium metaperiodate oxidizing system.

Our studies in the synthesis of sweetners based on readily available furan derivatives[1] required the preparation of furan and furfuralcarbonitriles. The literature methods available generally employ the corresponding aldehyde or carboxylic acid which is most often converted into its oxime[2] or amide[3] respectively and these are then dehydrated. More direct but less convenient methods include the ammonolysis of furfurals on vanadium-molybdenum catalyst[4] and the ring closures of 3-cyanopentan-2,4-diones[5]. The high-yielding, 'one-pot' conversions of the aldehyde into the nitrile function described by Olah and Keumi or Royer et al[6] have not been applied to furfurals. The work of Anderson et al[7] on pyrrole and Lohaus[8a] on thiophenes gave promise that direct cyanation of the furan nucleus might be achieved using chlorosulphonyl isocyanate (CSI). In the case of pyrrole[7a], CSI is added to a solution of the substrate in ethanonitrile and dimethylformamide (DMF) at -78°C, when the intermediate (2-pyrrolylcarbonyl)-sulphamoyl chloride 1 is converted into pyrrole-2-carbonitrile 2, as indicated in Equation 1. When a deactivating group is present in the 2-position of the pyrrole ring then the incoming sulphamoyl chloride group enters not at the 5- but at the 4- position, thus pyrrole-2-carboxaldehyde gives 4-cyanopyrrole-2-carboxaldehyde[7]. As with pyrrole, reaction of CSI with thiophene[8] followed by treatment of the intermediate with DMF results in the introduction of the carbonitrile group into the 2-position.

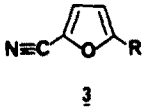


Equation 1.

Reaction of CSI with Furans

The cyanation of furan, using the same procedure as for pyrrole[7a], resulted in furan-2-carbonitrile, but in low yield. The yield was improved by delaying the addition of DMF until reaction between furan and CSI at -78°C was complete, or better still, if the order of addition was reversed and the furan added to a well stirred solution of CSI in ethanonitrile then DMF added as above. Using this "inverse

addition" procedure the results gathered in Table 1 were obtained. If both 2- and 5-positions of the furan nucleus were substituted as in 2,5-dimethylfuran the attack took place in the 3- position giving 6 in comparable yield (see Table 1) with the other examples. The reaction was unsuccessful using these conditions over the -25 to -78°C range for 2-furfural, 2-furfural protected as the 1,3-dioxolane and 1,3-dithiolane acetals, methyl 2-furoate, 2-furylacrylonitrile and 2-formyl-5-furfuryl methyl ether. It was clear therefore that the deactivation of the furan nucleus by the 2-carboxaldehyde and other electron withdrawing groups was too great for reaction to occur under the conditions employed as none of the expected product was observed and greater than 90% recoveries of 2-furfural achieved. This is in contrast with the chemistry of pyrrole[7] referred to above. The cyclic acetals underwent rapid deprotection by the reagent and again substantial recoveries of starting compound were made and none of the expected product detected. Prolonged reaction times and temperatures up to reflux in ethanonitrile failed to give the desired product, although recovery of starting material was substantially reduced.



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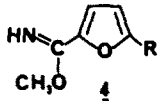

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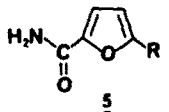

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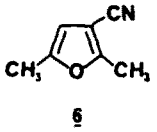

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a, R = -H c, R = $-CH_2OAc$ e, R = $-CH_2OCH_3$
b, R = $-CH_3$ d, R = $-CH_2OH$ f, R = -CHO

Hydrolysis of 2-cyano-5-furfuryl acetate, 3c.

As the direct cyanation of furfurals to give furfural carbonitriles was unsuccessful and in view of the availability of 3c the obvious alternative approach was by hydrolysis of 3c and oxidation of the alcohol 3d so produced. The attempted hydrolysis in aqueous ammoniacal methanol at RT for 16 hr, gave a stable white crystalline product in excellent yield having $M^{+\cdot}$ at m/e 155 and spectral data consistent with the amide 5e [IR, ν_{max} 3345, 1655 cm^{-1}; ^{1}H-NMR included 3.84 (s, 3H) and 8.3 (br, 2H, removed by D_2O); ^{13}C-NMR included 160.9 (s, 33)]. However, when furan-2-carbonitrile 3a was subjected to the same reaction conditions an analogous compound was the sole product isolated, which could only be methyl 2-furylimidate 4a. Thus making it clear that the hydrolysis product of 3c was correctly represented by the 2-furylimidate structure 4d. The hydrolysis of 3d in aqueous ammoniacal ethanonitrile at 50°C, gave the hydroxyamide 5d in 98% yield. The conversion of 3c to the corresponding alcohol 3d was eventually effected (81% yield) by hydrolysis in aqueous methanolic ammonia at RT for 2 hr.

Oxidation of the alcohol 3d to the aldehyde 3f.

Initial attempts using activated manganese dioxide in chloroform caused degradation of the furan ring, however, oxidation by pyridinium chlorochromate in dichloromethane or ruthenium dioxide and sodium metaperiodate in carbon tetrachloride gave very good (76 and 81% respectively) yields of the aldehyde. The last reagent is widely used in sugar chemistry for the oxidation of secondary alcohols to ketones.[9] It is usually found to be unsuitable for the oxidation of primary alcohols to aldehydes due to extensive oxidation of the aldehyde function to the carboxylic acid.[10] This is we believe the first report of a clean oxidation of this type. The ^{1}H and ^{13}C-NMR spectra of the furans described are collected in Table 1. Unambiguous assignments of the ^{13}C resonances are made on the basis of additivity of chemical shifts due to more than one functional group as illustrated by for example Gronowitz et al.[11] Good correlations are obtained (usually better than 1 p.p.m.) for the furans described, although the correlation for the trisubstituted furan 6 is less good (see Table 1) unless corrections for compression factors are applied.[12] The additivity values for the imino-ether substituent on the two position of the furan ring have not previously been reported

and are C_2, 17.8; C_3, 2.2; C_4, 1.5 and C_5, 2.0 relative to the furan carbon resonance positions of C_2, 142.6 and C_3, 109.6.[13]

EXPERIMENTAL

Organic extracts were dried over anhydrous magnesium sulphate. Distillations were carried out using a Kugelrohr apparatus. DCM = dichloromethane.

General Method for the cyanation of furans.

CSI (5.36 mM) in ethanonitrile (2 cm^3) was placed in a three necked flask fitted with thermometer, N_2 inlet and a pressure equalising funnel sealed with a rubber septum, the whole being set in a dry ice acetone bath. The furan (3.57 mM) in ethanonitrile (3 cm^3) was introduced via a syringe into the funnel and this solution was added dropwise to the vigorously stirred solution of CSI. The mixture was stirred (1 hr) and then DMF (1 cm^3) in ethanonitrile (1 cm^3) was added dropwise, allowed to reach RT, stood (1 hr) and then poured onto crushed ice. After extraction with DCM (3 x 15 cm^3), washing with $NaHCO_3$ (5%, 10 cm^3) followed by water (2 x 10 cm^3) the organic phase was dried and evaporated to give an oil which contained a little DMF. This was removed by passing down a short column of deactivated Al_2O_3 using ether as eluant. The oil obtained after evaporation of ether was distilled to give a pure colourless oil (see Table 1). 6 IR ν_{max} (liquid film) 3140, 2250, 1610, 1595 cm^{-1}. ^{1}H-NMR[14] 2.27 and 2.42 (3H, s), 6.04 (1H, s). MS[15] m/e (rel. int.) 121 (100), 120 (95), 106 (24), 78 (30).

2-cyano-5-furfuryl alcohol 3d.

To the acetate 3c (2.5 g, 15 mM) in MeOH (10 cm^3) at RT with stirring was added aqueous ammonia (0.880, 2.5 g, 50 mM). After 2 hr the MeOH was evaporated at the pump, the residue taken into DCM (10 cm^3) and the solution washed with water (3 x 5 cm^3), dried and the solvent evaporated. The residue was distilled to give a colourless oil (1.67 g, 13.6 mM). IR ν_{max} (liquid film) 3700-3000, 3140, 2250 cm^{-1}. ^{1}H-NMR 3.63 (1H, broad s removed by D_2O), 4.60 (2H, s), 6.45 and 7.11 (1H, d, J = 3.5 Hz). MS m/e (rel. int.) 123 (100), 122 (35), 106 (36), 78 (25), 68 (89), 64 (26), 51 (41), 39 (71).

5-cyano-2-furfural 3f. Method 1

To a stirred suspension of pyridinium chlorochromate (0.53 g, 2.45 mM) in DCM (10 cm^3) under N_2 was added a solution of 3d (0.20 g, 1.63 mM) in DCM (2 cm^3). After 2.5 hr the reaction mixture was filtered the residue being washed with ether. The combined organic phase was concentrated, filtered through florisil, evaporated and distilled to give a colourless oil (0.15 g, 1.24 mM). Method 2. To a suspension of RuO_2 (0.025 g, 0.19 mM) and $NaIO_4$ (0.10 g) in carbon tetrachloride (10 cm^3) was added 3d (0.100 g, 0.81 mM) in ether (2 cm^3) and the mixture stirred (16 hr). The mixture was filtered and the residue washed with ether. The solvent was evaporated and the residue distilled yielding a colourless oil (0.080 g, 0.67 mM). IR ν_{max} (liquid film) 3170, 3140, 2250, 1740 sh, 1700, 1590 cm^{-1}. ^{1}H-NMR 7.24 and 7.34 (1H, d, J = 3.5 Hz), 9.78 (1H, s). MS m/e (rel. int.) 121 (100), 120 (96), 64 (42).

Methyl 5-hydroxymethyl-2-furylimidate 4d.

A solution containing 3c (0.200 g, 1.21 mM) in 25% aqueous methanol (5 cm^3) and aqueous ammonia (0.880, 0.200 g, 4.0 mM) was kept at RT overnight. Methanol was evaporated and saturated brine (5 cm^3) added. The resulting oil was extracted into DCM (3 x 5 cm^3), the combined extracts washed with water and dried. The solid which remained on evaporation of solvent was recrystallized from a pet. ether (40-60°) - ether mixture giving white needles (0.160 g, 1.03 mM). IR ν_{max} (Nujol) 3345, 3745-3295, 1655 cm^{-1}. ^{1}H-NMR 3.7 - 8.0 (2H, broad s, removed by D_2O), 3.84 (3H, s), 4.57 (2H, s), 6.32 and 6.70 (1H, d, J = 3.5 Hz). MS m/e (rel. int.) 155 (45), 125 (49), 124 (39), 111 (34), 94 (100), 41 (37), 39 (34).

Using identical reaction conditions methyl 2-furylimidate 4a was obtained from furan-2-carbonitrile 3a. 4a IR ν_{max} (liquid film) 3350, 1655 cm^{-1}. ^{1}H-NMR 3.90 (3H, s), 6.44 (1H, dd, J = 3.5 and 1.5 Hz), 6.75 (1H, d, J = 3.5 Hz), 7.48 (1H, s, J = 1.5 Hz), 7.90 (1H, broad s, removed by D_2O). MS m/e (rel. int.)

125 (54), 95 (80), 94 (100), 81 (44), 67 (34), 39 (46), 32 (39).

5-Hydroxymethyl-2-furamide 5d.

A solution of the alcohol 3d (2.00 g, 16.26 mM), aqueous ammonia (0.880, 2.0 g, 40.0 mM) and ethanonitrile (10 cm^3) was warmed at 50°C for 24 hrs. Most of the solvent was evaporated and the solid residue recrystallized from aqueous methanol giving white needles (2.25 g, 15.90 mM). IR ν_{max} (Nujol) 3500-2600, 3350, 3180, 1665, 1605 cm^{-1}. ^{1}H-NMR (DMSO) 4.45 (2H, s), 5.4 - 5.9 (1H, broad s, removed by D_2O), 6.42 and 7.08 (1H, d, J = 3.5 Hz), 7.2 - 7.8 (2H, broad, removed by D_2O). MS m/e (rel. int.) 141 (66), 97 (100), 69 (32), 44 (23), 41 (53), 39 (29). Similarly, furan-2-carbonitrile 3a (2.00 g, 21.5 mM) was converted into furan-2-carboxamide 5a (1.80 g, 16.2 mM, 75%) m.p. 141-142°.

Acknowledgements

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14. ^{1}H-NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) at 100 MHz.
15. Mass spectra were determined at 70 eV on a VG 7070E instrument.

TABLE 1

	Furan	Yield(%)	mp or bpt	Found / Requires	C%	H%	N%	^{13}C-NMR ($CDCl_3$ at 25 MHz) C_2 [g]	C_3	C_4	C_5	C_2-subst.	Others		
1	3a	52	51°, 15 mm[a]					126.44 (s, 15)	122.0 (d, 54)	111.6 (d, 100)	147.5 (d, 64)	110.8 (s, 10)			
2	3b	60	71°, 15 mm[b]					124.6 (s, 15)	123.3 (d, 82)	107.9 (d, 100)	158.2 (s, 20)	111.8 (s, 10)	13.7 (q, 72)		
3	3c	72	79°, 0.1 mm[c]					126.3 (s, 16)	122.9 (d, 80)	111.5 (d, 88)	155.1 (s, 31)	111.2 (s, 12)	20.5 (q, 55)	57.3 (t, 100)	170.1 (s, 16)
4	6	49	78°, 0.1 mm	Found	69.8	5.9	11.7	159.9 (s, 20)	94.5 (s, 10)	106.6 (d,88)	151.9 (s, 23)	13.0[e] (q, 100)	114.3 (s, 10)		
				C_7H_7NO: Requires	69.4	5.8	11.6								
5	3d	90	81°, 0.1 mm	Found	58.3	4.3	11.3	125.4 (s, 14)	123.4 (d, 79)	108.9 (d, 100)	160.0 (s, 29)	111.6 (s, 8)	56.9 (t, 65)		
				$C_6H_5NO_2$: Requires	58.5	4.1	11.4								
6	3f	76(81)[d]	80°, 0.1 mm	Found	59.5	2.5	11.6	154.7 (s, 11)	118.7 (d, 100)	123.0 (d, 95)	129.6 (s, 12)	177.9 (d, 78)	110.2 (s, 9)		
				$C_6H_3NO_2$: Requires	59.5	2.6	11.6								
7	4a	74	50°, 15 mm	Found	57.7	5.8	11.3	160.4 (s, 8)	111.8 (d, 90)	111.1 (d,69)	144.6 (d,100)	145.7 (s, 15)	52.9 (q, 71)		
				$C_6H_7NO_2$: Requires	57.6	5.6	11.2								
8	4d	85	83-85°	Found	54.1	5.7	8.9	160.9 (s, 33)	112.6 (d, 73)	109.5 (d, 100)	157.9 (s, 33)	144.6 (s, 24)	53.3 (q, 86)	56.7 (t, 87)	
				$C_7H_9NO_3$: Requires	54.2	5.8	9.0								
9	5d	98	135-136°	Found	51.3	5.2	10.1	147.3 (s, 32)	116.9 (d, 84)	110.7 (d, 90)	158.7 (s, 80)	161.9 (s, 29)	56.8[f] (t, 100)		
				$C_6H_7NO_3$: Requires	51.1	5.0	9.9								

a, 146-148°, 760 mm, O. Wallah, Ann., 1882, 214, 227.

b, 78-80°/20 mm, M.M. Runde et. al., J.A.C.S., 1930, 52, 1284.

c, 140°(bath temp.)/0.01 mm, F.H. Newth and L.F. Wiggins, J. Chem. Soc., 1947, Part 1, 396.

d, Method B (see Experimental)

e, Methyl resonances are coincident.

f, DMSO solvent.

g, Numbering follows IUPAC system