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Conversion of Formyl into Cyano Groups in Kojic Acid Derivatives and Analogues

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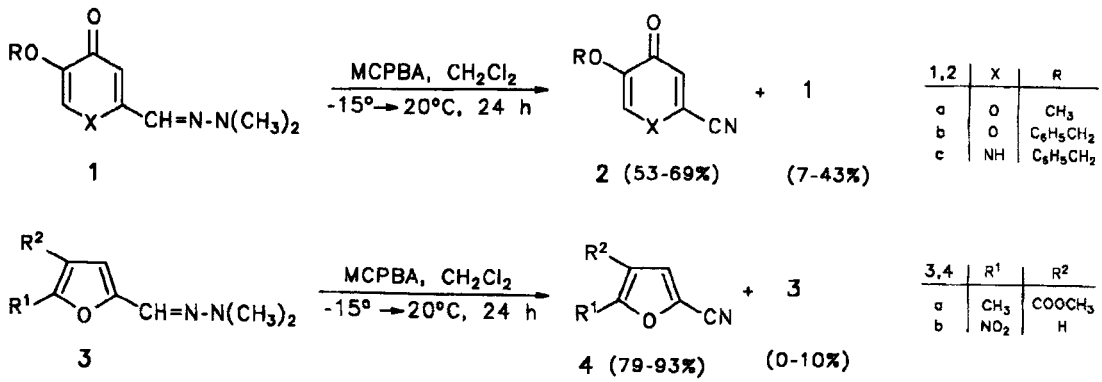
Abstract. It has been revealed that N,N-dimethylhydrazones (**1a-c**, **3a,b**) derived from kojic acid analogs, such as substituted furans (**3a,b**), 4-pyrones (**1a,b**) and 4-pyridine (**1c**), on oxididation with 3-chloroperoxybenzoic acid afford the corresponding nitriles (**2a-c**, **4a,b**). The method has preparative value. The mechanism of the reaction is presented.

Oxidation of N,N-dimethylhydrazones has been reported as a useful method for the synthesis of nitriles [1–4]. In our previous work it has been shown that hydrogen peroxide in the presence of 2-nitrobenzeneseleninic acid as catalyst is a convenient oxidant for N,N-dimethylhydrazones derived from aromatic aldehydes [2]. Most recently it has also been revealed that aliphatic and heteroaromatic nitriles could be prepared when 3-chloroperoxybenzoic acid (MCPBA) is used as an oxidant [4] The main aim of the present work was the synthesis of nitriles derived from more complex heterocyclic systems, such as substituted 4-pyrones, 4-pyridones, and furans. The first of them were derivatives of 5-hydroxy-2(hydroxymethyl)-4H-pyran-4-one (kojic acid), an important product of biotransformation of various carbohydrates. These nitriles, being potential substrates for further syntheses, remained unknown (except 2-nitrofuran-5-carbonitrile [5] since they were not available by classical methods, such as dehydration of oximes, because other competitive reactions take place. These multifunctional compounds, as well as substituted furans, seemed to be good models to test the chemoselectivity of the oxidative conversion of N,N-dimethylhydrazones into nitriles.

The starting 5-substituted-4-oxo-4H-pyrane-2-carbaldehydes and 4-oxo-1,4-dihydropyridine-2-carbaldehyde were prepared by oxidation of the hydroxymethyl group in the corresponding heterocyclic alcohols in xylene or dioxane [6]. 2-Formyl-5-nitrofuran was obtained from 2-furancarbaldehyde by nitration of its diacetate [7], and 2-formyl-4-carboxy-methyl-5-methylfurane, a new compound, by formylation of 2-methyl-3-carboxymethyl-furan. The aldehydes treated with N,N-dimethylhydrazine yielded N,N-dimethylhydrazones **1a–c** and **3a,b**, which were isolated and oxidized with MCPBA in methylene chloride. The reactions proceeded according to Scheme 1; the products were isolated using column chromatography. The nitriles were accompanied by unreacted substrates which could be used again. The molar ratio of oxidant to substrate varied in the range of 2.2–3.5, but in Table 2 and the experimental part only optimal results are given. When the oxidant was used in substantial excess, the nitrile yield was slightly higher but the product was accompanied with by-products making isolation and purification of nitriles more troublesome. The results show that the method presented is highly chemoselective and can be used as an alternative when dehydration of oximes does not work. It seems to be more convenient for the synthesis of 2-nitrofuran-5-carbonitrile than the methods reported earlier [5, 8–11]. In pyrone derivatives no isomerisation of the 4-pyrone system into the 2-pyrone one was observed.

It was found that, when N,N-dimethylhydrazone **3b** was oxidized, hexahydro-1,3,5-trihydroxy-1,3,5-triazine **7** was formed in 25% yield. The same compound **7** was



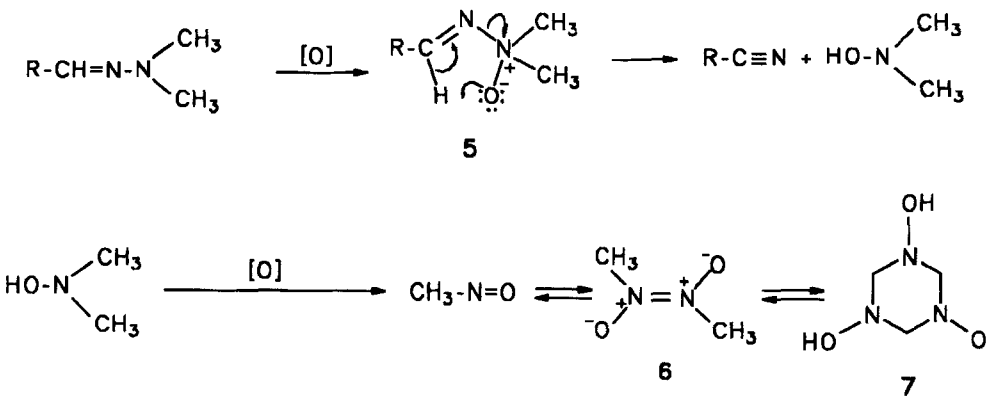
Scheme 1

detected as admixture in crude nitriles **2a**, **2c**, **4a** and **4b** by ^{1}H-NMR spectroscopy where signals of CH_3 protons (3.97 ppm) were observed. Its melting point was identical to that of hexahydro-1,3,5-trihydroxy-1,3,5-triazine mentioned earlier in ref. [12, 13], and the OH bands in the IR (KBr) spectrum was observed. Although compound **7** can be regarded as a trimer of the unstable formaldoxime or its tautomer nitrosomethane, the presence of CH_3 protons and lack of OH protons in the ^{1}H-NMR spectrum measured in deuterated chloroform suggests that in solution the dimeric form **6** predominates. The absorption band (λ_{max} 285 nm) in the UV spectrum measured in chloroform characteristic of the azadioxy group [14] confirmed the dimeric structure **6** existing in the solution. When a GC/MS spectrum was taken, hexahydro-1,3,5-trihydroxy-1,3,5-triazine **7** decomposed to a monomer which was identified as nitrosomethane. These results throw an additional light on

Table 1 N,N-Dimethylhydrazones (**1,3**) and hexahydro-1,3,5-trihydroxy-1,3,5-triazine (**7**)

No.	Y.%	m.p.°C	IR [a]	UV [b]	MS (m/e)	^{1}NMR ($CDCl_3$/TMS) δ (ppm)
1a	71	119-122	1650 [c] 1585 [d]	342 (3.77)	196 (100,M^+), 178 (2,M^+–H_2O), 167 (6,M^+–CHO, 166 (2,M^+–CH_2O), 152 (16), 109 (10), 97 (13), 96 (31), 95 (61)	3.14 (s, 6H, CH_3-N), 3.77 (s, 3H, CH_3-O), 6.44 (s, 1H, H-3), 6.61 (s, 1H, CH=N), 7.50 (s, 1H, H-6)
1b	81	121-123	1623 [c] 1571 [d]	343 (3.72)	272 (40,M^+), 228 (2), 195 (10, M^+–C_6H_5), 166 (16,M^+–PhCHO),96 (10), 95 (20), 91(100, $PhCH_2$)	3.10 (s, 6H, CH_3–N), 5.07 (s, 2H, CH_2Ar),6.43 (s, 1H, H-3), 6.56 (s, 1H, CH=N), 7.35 (5H,C_6H_5), 7.46 (s, 1H, H-6)
1c	83	223-226	2696 [e] 1621 [c] 1567 [d]	320.5 (3.65) – 191 (3.53)	–	3.10 (s, 6H, CH_3–N), 5.05 (s, 2H, CH_2Ar), 6,50 (s, 1H, CH=N, 6.93 (s, 1H, N-H),), 7.3–7.6 (m, 7H, C_6H_5, H-3 and H-6) [f]
3a	68	oil	1717 [c] 1596 [d]	302 (3.62)	210 (100,M^+), 195 (23,M^+–CH_3), 179 (7, M^+–OCH_3), 177 (4,M^+–CH_3,H_2O), 163 (6),152 (8),140 (7), 137 (9), 135 (15), 125 (4), 121 (5), 109 (4), 108 (8), 107 (10)	2.26 (s, 3H, CH_3C=), 2.97 (s, 6H, CH_3–N), 3.82 (s,3H,CH_3–O), 6.55 (s, 1H, 3-FurH), 6.99 (s, 1H, CH=N)
3b	73	113-114 Ref.[16] 110-111	1541 [d] 1323 [g]	280 (3.34) 426 (3.54)	183 (100,M^+), 167 (1,M^+–O), 166, (1,M^+–HO), 153 (6,M^+–NO), 137 (1), 135 (2), 125 (M^+–CO, NO), 110 (6), 109 (45),98 (36)	3.13 (s, 6H, CH_3–N), 6.57 (d, J=4 Hz,1H, ArH), 6.92 (s, 1H, CH=N), 7.36 (d, J=4Hz, 1H, ArH)
7	25	112,5-114,5 Ref.[12] 114-115	3433 [h]	285 (4.05) [i] Ref.[15] 286 (4.05)	45 (100,M^+,CH_3N=O), 44 (16), 43 (27), 42 (11), 30 (100,M^+–CH_3)	3.97 (s, 6H, CH_3–N)

[a]) in KBr, cm^{-1} [b]) λ_{max} [nm] (log ε), in EtOH [c]) $\nu_{C=O}$ [d]) $\nu_{C=N}$ [e]) $\nu_{O-H...O}$
[f]) 1H-NMR in CD_3OD [g]) ν_{NO} [h]) ν_{OH} [i]) in $CHCl_3$



Scheme 2

the mechanism of the oxidative conversion of N,N-dimethylhydrazones into nitriles where dimethylhydroxylamine was postulated as a final molecule eliminated from the intermediate N-oxide **5** [15]. Our results give the evidence that dimethylhydroxylamine is subsequently oxidized to nitrosomethane according to Scheme 2.

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Experimental

Melting points: Digital Melting Point Apparatus Electrothermal IA 9100. UV: Hewlett-Packard 8452 A diode array spectrometer. – IR 75 infrared spectrometer. – GC/MS: Hewlett-Packard 5890 apparatus with capillary column HP-1, 25m, 0.2 mm. – ^{1}H-NMR: Tesla 80 MHz spectrometer. All new compounds gave satisfactory microanalyses.

Table 2 4-Oxo-4H-pyrane-2-carbonitriles (**2a,b**), 5-Benzyloxy-4-oxo-1,4-dihydropyridine-2-carbonitrile (**2c**) and 2-Nitrofuran-5-carbonitriles (**4a,b**)

No.	Q[a]	Y[b]	U[c]	m.p.°C	IR[d]	MS (m/e)	^{1}H-NMR CDCl3/TMS δ (ppm)
2a	2.2	63	23	145–146 benzene	2249 [e] 1637 [f]	151 (100,M^+), 150 (26,M^+–H), 133 (19,M^+–H_2O), 123 (5,M^+–CO), 122 (31M^+–CHO), 121 (80,M^+–CH_2O), 120 (11,M^+–OCH_3), 108 (2.5), 105 (2.5), 97 (1), 96 (10), 95 (41) M^+–CH_2O and CN), 94 (47), 93 (34,M^+–CH_2O and CO), 92 (2)	3.81 (s, 3H, CH_3–O) 6.88 (s, 1H, H-3) 7.63 (s, 1H, H-6)
2b	2.2	56	38	149.8–150.2 CH_2Cl_2	2243 [e] 1644 [f]	227 (5,M^+), 121 (3,M^+–C_6H_5CHO), 105 (2,M^+–C_6H_5COOH), 93 (1,M^+–C_6H_5CHO and CO), 92 (8), 91 (100, $C_6H_5CH_2$), 90 (3), 89 (6)	5.10 (s, 2H, CH_2–O) 6.88 (s, 1H, H-3) 7.37 (s, 5H, C_6H_5) 7.57 (s, 1H, H-6)
	3.5	65	0				
2c	2.2	53	43	165–166 CH_3Cl/ n-hexane	3522 [g] 2237 [e]	–	5.25 (s, 2H, CH_2–O) 7.27 (s, 1H, H-3 or H-6) 7.29 (s, 1H, H-3 or H-6) 7.42 (s, 5H, C_6H_5) 8.26 (s, 1H, N-H)
	3.5	69	7	1:10	1578 [f,h]		
4a	2.2	79	10	64.5–65.5 n-pentane	2238 [e] 1728 [f]	165 (35,M^+), 150 (21,M^+–CH_3), 135 (85),134 (100,M^+–OCH_3) 133 (21), 123 (1), 122 (2), 106 (2), 105 (6)	2.66 (s, 3H, CH_3C=), 3.86 (s, 3H, CH_3–O), 7.33 (s, 1H, 3-FurH)
4b	2.5	93	0	63.3–64.2 Et_2O Ref.[5] 63-65	2241[e] 1386 [i]	138 (66,M^+), 122 (4,M^+–O), 109 (4), 108 (80,M^+–NO), 94 (1), 81 (2), 80 (41,M^+–NO and CO),65 (4.6), 64 (100), 63 (30), 62 (10), 55 (2.9), 54 (62)	7.30 (d,J=3.8Hz, 1H, ArH) 7.39 (d, J=3.8Hz, 1H, ArH)

[a]) Oxidant/substrate ratio (mmol/usual) [b]) Yield, % nitrile [c]) % Unreacted substrate
[d]) in KBr, cm^{-1} [e]) $\nu_{C\equiv N}$ [f]) $\nu_{C=O}$ [g]) ν_{N-H} [h]) in $CDCl_3$ [i]) ν_{NO2}

4-Carboxymethyl-5-methyl-2-furaldehyde

Phosphorus oxychloride (27.9 g, 0.3 mole) was added to N,N-dimethylformamide (30 ml) with stirring and ice-cooling during 15 min. After storage at 25 °C for 1 h 2-methyl-3-carboxymethylfuran (42.05 g, 0.3 mole) was added with stirring at 25 °C within 20 min. The solution was heated to 100 °C for 3 hrs, then cooled and poured into a solution of sodium carbonate (25 g) in water (250 ml) during 10 min at a temperature below 20 °C. The mixture was stirred, and after addition of solid sodium carbonate (80 g) in small portions was left to stand at room temperature for 12 hrs. The mixture was extracted with chloroform (3×100 ml), the organic layers were combined, washed with water, dried with sodium sulfate and evaporated to dryness. The residue recrystallized from cyclohexane afforded pure aldehyde (46.4 g, 92%) as a pale yellow crystalline solid m.p. 79-81°C.
^{1}H-NMR: δ (ppm)/$CDCl_3$ 2.70 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3) 7.49 (s, 1H, 3-FurH), 9.57 (s, 1H, CHO).

$C_8H_8O_4$	Calcd.	C 57.14	H 4.80
(168.15)	Found	C 57.03	H 4.77

Synthesis of N,N-Dimethylhydrazones (1,3)

A stirred solution of aldehyde (10 ml) in toluene (40 ml) containing catalytic amount of TsOH (15 mg) was treated with N,N-dimethylhydrazine (0.61 g, 10 mmol) with cooling in an ice-salt bath. Then, the solution was refluxed for 4 hrs, and the water evolved was removed in a Dean-Stark trap. The solvent was evaporated in vacuo and the crude N,N-dimethylhydrazone (**1a-c**, **3b**) was recrystallized from the toluene or characterized as an oil (**3a**).

Synthesis of nitriles (2, 4)

The solution or suspension of N,N-dimethylhydrazone (**1**, **3**) (1.0 mmol) in methylene chloride (10 ml) was cooled in an ice-salt bath to −15 °C under vigorous stirring and 3-chloroperoxybenzoic acid (55%) (0.69–1.10 g, 2.20–3.50 mmol, Table 2) in methylene chloride (30–40 ml) was added dropwise within 4 hrs. The reaction was continued at room temperature for 18 hrs. After this period, anhydrous potassium carbonate (0.6–0.9 g, 4.3–6.5 mmol) was added, and the mixture was stirred until gas evolution stopped. The solid was filtered off, extracted with methylene chloride (5×25 ml), and the solvent was evaporated in vacuo. The residue was dissolved in chloroform and chromatographed on a silica-gel column using chloroform (for **2a,b** and **4a,b**) or chloroform-ethyl acetate 4:1 (for **2c**) as an eluent. After separation of the first fractions containing nitrile, unreacted starting N,N-dimethylhydrazones were eluted with chloroform-ethyl ether 20:1 (**1a**, **3a**), chloroform-methanol 20:1 (**1b**) or ethyl acetate-methanol 4:1 (**1c**). The nitriles **2**, **4** were recrystallized from solvents given in Table 2. Nitrile **4a** was also isolated by an alternative way: The crude product was extracted with boiling hexane (5×1 ml), the solvent was evaporated in vacuo and the residue recrystallized from pentane giving pure **4a** in 78% yield. After separation of the nitrile **4b** on the silica-gel column, the last fractions were collected, chloroform was evaporated in vacuo and the residue recrystallized from methylene chloride to give pure hexahydro-1,3,5-trihydroxy-1,3,5-triazine **7**.

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