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Derivatives and Reactions of Glutacondialdehyde. Part 3. 1-Aryl-3-formyl-2(1*H*)-pyridinethiones from the Glutacondialdehyde Anion and Aryl Isothiocyanates

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1-Aryl-3-formyl-2(1*H*)-pyridinethiones have been synthesized from the glutacondialdehyde sodium salt and aryl isothiocyanates. The course of the reaction may be understood on basis of the concept of hard and soft acids and bases.

Ring closure reactions of glutacondialdehyde derivatives have been reported. Thus, pyridines,[1] pyrylium perchlorate,[2] and some nicotinaldehyde derivatives [3] have been prepared from the appropriate reagents. In connection with a current investigation [4] of the properties of the glutacondialdehyde anion (*1*) we report in this paper a high yield synthesis of 1-aryl-3-formyl-2(1*H*)-pyridinethiones (*2*) from *1* and aryl isothiocyanates (*cf.* Scheme 1).

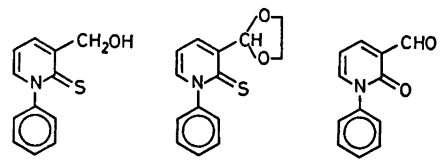
RESULTS

1 *2*

R	R
2a phenyl	*2f* 2′,6′-dimethylphenyl
2b 3′-methylphenyl	*2g* 2′,6′-dichlorophenyl
2c 3′-fluorophenyl	*2h* 1′-naphthyl
2d 4′-fluorophenyl	*2i* 2′-naphthyl
2e 2′-methoxycarbonylphenyl	

Scheme 1.

Due to the low solubility of the salt (*1*) in organic solvents of low polarity, the exothermic reactions were run in *N*,*N*′-dimethylformamide or dimethyl sulfoxide at 25 °C.



3 *4* *5*

Identification. The derivatives *3*, *4*, and *5* were prepared from *2a* by standard methods. By comparing the UV spectra of *3*, *4*, and 1-phenyl-2(1*H*)-pyridinethione it was evident that the same chromophore was present in all three compounds (*cf.* Experimental Section). The IR and MS spectra of *2* further supported the 3-formyl-2(1*H*)-pyridinethione structure. However, based on the information from these spectra and the way of synthesis it seemed impossible to decide definitely whether the formyl group was attached to carbon atom 3 or 6.

^1H NMR spectra. In the ^{1}H NMR spectra of *2* an ABX system was observed (*cf.* Table 1). The magnitudes of the coupling constants $J_{4,5}$ and $J_{5,6}$ were as expected for a 3-substituted 2(1*H*)-pyridinethione or -one.[5] However, both in *2* and *5* the difference between the *ortho* couplings were smaller than predicted [5] and therefore the 6-substituted isomer was not completely excluded.

Table 1. 1-Aryl-3-formyl-2(1*H*)-pyridinethiones from the glutacondialdehyde anion and aryl isothiocyanates $J_{4,5}=J_{5,6}=6.8$ Hz and $J_{4,6}=1.5$Hz for *2a–2i*.

Compound[a]	Yield %	M.p. °C	^{1}H NMR chemical shifts (DMSO-d_6, δ) H(4)	H(5)	H(6)	CHO	Other
2a	95	180–182[b]	7.90	6.98	8.35	10.56	7.3–7.7 (aryl
2b	79	173–175[c]	7.76	6.84	8.20	10.38	7.1–7.3 (aryl), 2.35 (methyl)
2c	97	171–173[b]	7.88	6.93	8.35	10.50	7.2–7.7 (aryl)
2d	82	191–193[c]	7.78	6.86	8.24	10.37	7.3–7.4 (aryl)
2e	52	214–217[c]	7.75	6.95	8.34	10.46	7.4–8.0 (aryl), 3.65 (methyl)
2f	79	190–192[c]	7.99	7.00	8.19	10.54	7.2 (aryl), 2.00 (methyl)
2g	45	259–260[d]	Insoluble				
2h	87	201–204[c]	–	7.06	8.43	10.62	7.4–8.3 (aryl and H(4))
2i	94	195–196[d]	–	6.95	8.43	10.44	7.4–8.1 (aryl and H(4))

[a] *Cf.* Scheme 1. [b] Recrystallized from benzene. [c] Recrystallized from toluene. [d] Recrystallized from 2-methoxyethanol.

The resonance of one of the ring protons was observed within the range δ 8.19–8.35 (*cf.* Table 1). This is in accordance with chemical shift values reported for the 6-proton in 2(1*H*)-pyridinethiones.[5]

^{13}C NMR analyses. The assignments of the chemical shifts for the carbon atoms in *2a* and 1-phenyl-2(1*H*)-pyridinethione were confirmed by selective decoupling experiments (*cf.* Fig. 1). The observed formyl group substituent effects are in agreement with results reported for pyridines and benzenes.[6]

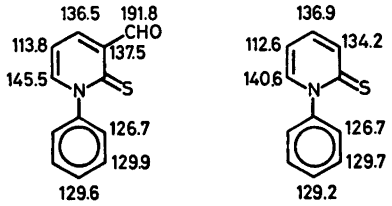


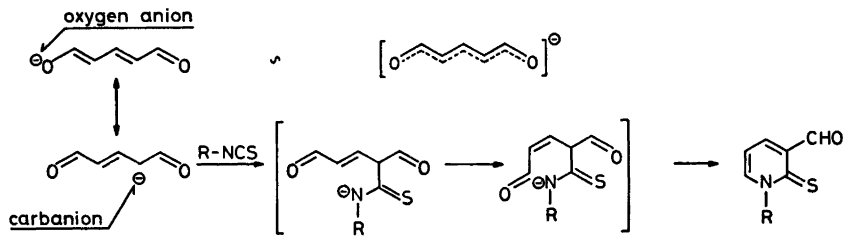
Fig. 1. ^{13}C NMR chemical shifts of 1-phenyl-3-formyl-2(1*H*)-pyridinethione and 1-phenyl-2(1*H*)-pyridinethione (δ, DMSO-d_6).

In the undecoupled spectrum of *2a* a J_{C-H} coupling constant of 183.8 Hz was observed. The magnitude of this coupling constant is in agreement with values reported for $J_{C(6)-H}$ in pyridines [6] and establishes that C(6) in the product *2* is unsubstituted.

DISCUSSION

The reaction of the glutacondialdehyde anion and aryl isothiocyanates gives rise to new and potentially useful pyridine derivatives, which are inaccessible by known procedures; *e.g.* arylation of 2(1*H*)-pyridinethiones is generally not possible.[7] The probable reaction mechanism is shown in Scheme 2.

Ring closure reactions involving isothiocyanates are well-known. However, it may seem surprising that the reaction takes place at carbon number 2 in the glutacondialdehyde



Scheme 2.

anion, but molecular orbital calculations indicate a relatively high electron density at this position.[8]

The reaction course may be understood on basis of the principle of hard and soft acids and bases (HSAB).[9] In the ambident anion, *1*, the carbanion center [C(2)] is a softer base than the oxygen anion center (RO^-, *cf.* Scheme 2). The carbon atom in the isothiocyanato group represents a soft acid. Consequently, the HSAB principle predicts the reaction to take place at C(2). The subsequent cyclization forming the stable 1-aryl-3-formyl-2(1*H*)-pyridinethiones is exceptable.

EXPERIMENTAL

Microanalyses were carried out in the Microanalytical Department of the University of Copenhagen. Satisfactory elemental analyses (±0.3 %) were obtained for all new compounds.

Instrumentation. IR: Perkin Elmer 457. UV: Beckman ACTA III. ^{1}H NMR: Jeol C-60HL and Bruker HX-60. MS: AEI MS-902. ^{13}C NMR: Varian XL-100 F-15FT. The melting points are uncorrected.

General procedure for the preparation of *1-aryl-3-formyl-2(1H)-pyridinethiones (2).* The sodium salt of glutacondialdehyde (*1*) (0.01 mol) in DMSO (10 ml) or DMF and the appropriate aryl isothiocyanate[10] (0.01 mol) were mixed with stirring at room temperature. After 2 h the reaction mixture was added to water (100 ml) and the precipitated orange crystals were isolated, dried and recrystallized (Table 1). In the mass spectra of *2a* to *2i* relative abundant molecular ions were observed. The [M − 29]* ion gave rise to the base peak in all cases. In the IR spectra bands at *ca.* 1100 cm^{-1} (NCS)[11] support structure *2*. UV (ethanol) of *2a*: λ_{max} nm (log ε) = 385 (3.49), 321 (3.99) and 298 sh (3.78).

1-Phenyl-3-hydroxymethyl-2(1H)-pyridinethione (3). 2a (1.0 g) and sodium borohydride (0.5 g) in dioxane (60 ml) were stirred overnight at room temperature. Addition of water (600 ml) and extraction with ether yielded an oil which upon trituration with ether gave *3* (0.42 g). Recrystallization from water gave yellow needles, m.p. 140 − 142 °C.

NMR (DMSO-d_6): δ 7.73 [H(4)], 6.99 [H(5)], 8.04 [H(6)], 7.2 − 7.6 (phenyl), 4.53 (CH_2) and 5.30 (OH); $J_{4,5}$ = 6.9, $J_{5,6}$ = 6.5 and $J_{4,6}$ = 1.8 Hz. UV (ethanol): λ_{max} nm = 368 (log ε = 3.85), 286 (log ε = 4.05) and 238 (sh, log ε = 3.90). IR (KBr) ν_{max} cm^{-1} = 3350 (OH). MS: *m/e* = 217 (100 %, M).

1-Phenyl-3-[2'-(1',3'-dioxalanyl)]-2(1H)-pyridinethione (4). 2a (26.4 g), 1,2-ethanediol (40 g) and *p*-toluenesulfonic acid (0.5 g) in dry benzene (1.2 l) were refluxed (with water separator). When 8 ml water had been collected, the reaction mixture was evaporated *in vacuo* to give *4* (24.3 g). Recrystallization from cyclohexane-benzene yielded yellow needles, m.p. 163 − 165 °C.

NMR (DMSO-d_6): δ 7.73 [H(4)], 6.91 [H(5)] 8.10 [H(6)], 7.3 − 7.6 (phenyl), 6.41 (CH) and 4.03 (CH_2); $J_{4,5}$ = 7.2, $J_{5,6}$ = 6.5 and $J_{4,6}$ = 1.8 Hz. UV (ethanol): λ_{max} nm = 378 (log ε = 3.94), 293 (log ε = 4.33) and 236 (sh, log ε = 4.05). MS: *m/e* = 259 (67 %, M) and 186 (100 %).

1-Phenyl-3-formyl-2(1H)-pyridone (5). 2a (8.6 g) and mercury(II) oxide (19.5 g) were refluxed in abs. ethanol (750 ml) for 5 h. After filtration of the black reaction mixture and concentration *in vacuo* a semicrystalline red compound (8.5 g) was obtained. Trituration with benzene yielded *5* (1.2 g). Recrystallization from toluene yielded *5* as pale yellow crystals, m.p. 155 − 157 °C.

NMR (DMSO-d_6): δ 8.08 [H(4)], 6.57 [H(5)], 8.19 [H(6)], 7.5 (phenyl) and 10.15 (CHO). $J_{4,5}$ = 7.2, $J_{5,6}$ = 6.5 and $J_{4,6}$ = 2.3. UV (ethanol): λ_{max} nm = 360 (log ε = 3.82) and 238 (sh, log ε = 4.01). IR (KBr): ν_{max} cm^{-1} = 2855 (CHO). 1689 (CHO) and 1660 (2(1*H*)-pyridone). MS: *m/e* = 199 (28 %, M) and 171 (100 %).

1-Phenyl-2(1H)-pyridinethione. 1-Phenyl-2(1*H*)-pyridone[12] (0.7 g) was heated with phosphorus pentasulfide at 170 °C for 6 h. Addition of 4 N sodium hydroxide, extraction with chloroform, concentration *in vacuo* and recrystallization from cyclohexane yielded yellow crystals, m.p. 102 − 104 °C (31 %).

NMR(DMSO-d_6): δ 6.85 (H(5)), 7.98 [H(6)], 7.3 − 7.7 [H(3), H(4) and phenyl]; $J_{4,5}$ = 6.0, $J_{5,6}$ = 6.0, $J_{4,6}$ = 1.2 and $J_{3,5}$ = 2.3 Hz. UV (ethanol): λ_{max} nm = 371 (log ε = 3.76), 292 (log ε = 4.01) and 234 (sh, log ε = 3.81). MS: *m/e* = 187 (100 %, M$^+$).

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