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SHORT COMMUNICATIONS

A Simple and Efficient Route to Substituted 2-Alkylsulfanyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles

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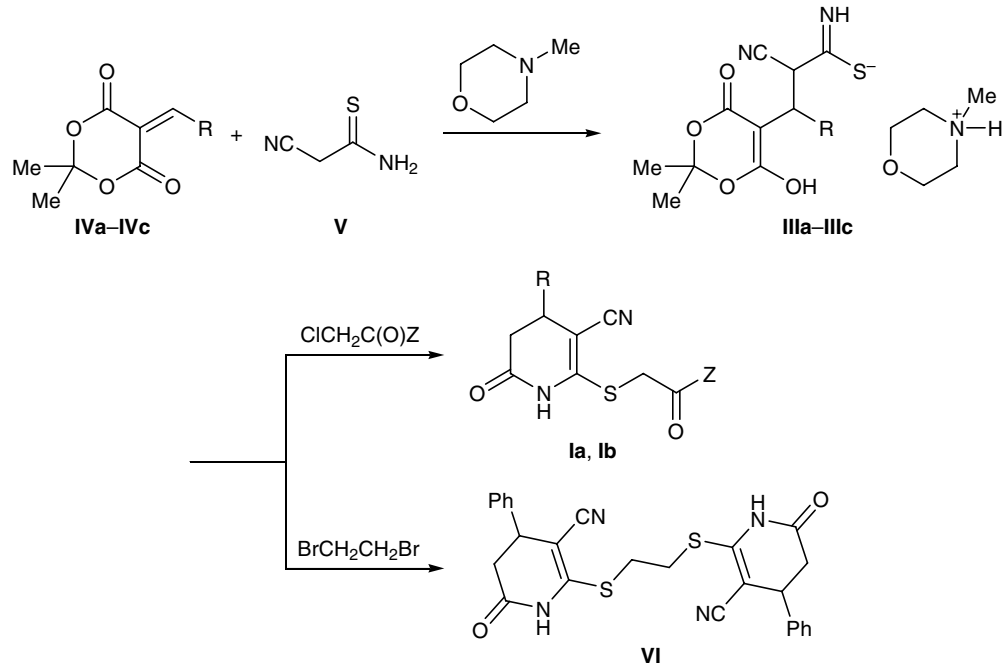
Substituted 6-alkylsulfanyl-1,2,3,4-tetrahydropyridines were synthesized previously by alkylation of the corresponding ammonium tetrahydropyridine-6-thiolates [1]. 2-Alkylsulfanyl-4-aryl(hetaryl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**I**) are potential intermediate products for the synthesis of dyes [2]. The present communication reports for the first time on the synthesis of compounds **I** by heating chloroacetic acid derivatives **II** with Michael adducts **III** in ethanol for a short time. Compounds **III** were prepared in turn by reaction of 5-aryl(hetaryl)methylidene-2,2-dimethyl-1,3-dioxane-4,6-diones **IV** with cyanothioacetamide (**V**) in the presence of *N*-methylmorpholine. The alkylation of salt **IIIb** with 1,2-dibromoethane afforded 2,2'-ethylenedisulfanylbis(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile) (**VI**).

***N*-(4-Bromophenyl)-2-[3-cyano-6-oxo-4-(2-thienyl)-1,4,5,6-tetrahydropyridin-2-ylsulfanyl] acetamide (Ia).** A mixture of 4.40 g (10 mmol) of salt **IIIa** and 2.49 g (10 mmol) of *N*-(4-bromophenyl)-chloroacetamide (**IIa**) in 30 ml of ethanol was heated for 5 min under reflux. The mixture was filtered while hot through a folded filter, the filtrate was cooled, and the precipitate was filtered off and washed with ethanol and hexane. Yield 3.22 g (72%), white powder,



I, R = 2-thienyl, Z = 4-BrC_6H_4NH (**a**), R = 3-EtO-4-HOC_6H_3, Z = $PhCH_2O$ (**b**); **II**, Z = 4-BrC_6H_4NH (**a**), $PhCH_2O$ (**b**); **III**, **IV**, R = 2-thienyl (**a**), Ph (**b**), 3-EtO-4-HOC_6H_3 (**c**).

mp 220–224°C (from AcOH). IR spectrum, ν, cm^{-1}: 1671 (C=O), 2212 (C≡N). ^1H NMR spectrum, δ, ppm: 2.70 d and 2.99 d (1H each, 5-H, J = 10.82 Hz), 3.89 s (2H, SCH_2), 4.21 m (1H, 4-H), 6.92 m (2H, 3'-H, 5'-H), 7.24 d.d (1H, 4'-H, J = 5.94 Hz), 7.39 d and 7.56 d (2H each, C_6H_4, J = 7.53 Hz), 10.38 br.s (1H, NH), 10.57 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 450 (9) $[M + 2]^+$, 449 (8) $[M + 1]^+$, 448 (4) $[M]^+$, 276 (11), 174 (49), 138 (63), 122 (14), 111 (40), 99 (100), 98 (27). Found, %: C 48.01; H 3.00; N 9.15. $C_{18}H_{14}BrN_3O_2S_2$. Calculated, %: C 48.22; H 3.15; N 9.37. M 448.36.

Benzyl 2-[3-cyano-4-(3-ethoxy-4-hydroxyphenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-ylsulfanyl]-acetate (Ib) was synthesized in a similar way from 4.33 g (10 mmol) of salt **IIIb** and 1.52 ml (10 mmol) of benzyl chloroacetate (**IIb**). Yield 2.80 g (64%), colorless needles, mp 133–135°C (from EtOH). IR spectrum, ν, cm^{-1}: 1682 (C^6=O), 1744 (C=O, ester), 2204 (C≡N), 3416 (OH). ^1H NMR spectrum, δ, ppm: 1.31 t (3H, C**H**$_3$CH$_2$, J = 6.19 Hz), 2.49 d.d and 2.61 d.d (1H each, 5-H, J = 10.99 Hz), 3.80 m (1H, 4-H), 3.95 q (2H, OC**H**$_2$CH$_3$, J = 6.19 Hz), 4.00 d and 4.11 d (1H each, SCH_2, ^2J = 18.09 Hz), 5.10 d and 5.18 d (1H each, OC**H**$_2$Ph, ^2J = 17.16 Hz), 6.52 d (1H, H_{arom}, J = 7.12 Hz), 6.71 m (2H, H_{arom}), 7.32-7.41 m (5H, H_{arom}), 8.95 br.s (1H, NH), 11.58 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 439 (8) $[M + 1]^+$, 438 (6) $[M]^+$, 424 (5), 333 (14), 245 (12), 175 (16), 154 (27), 138 (84), 122 (25), 111 (30), 99 (100). Found, %: C 62.81; H 4.97; N 6.20. $C_{23}H_{22}N_2O_5S$. Calculated, %: C 63.00; H 5.06; N 6.39. M 438.51.

***N*-Methylmorpholinium 2-cyano-3-(4-hydroxy-2,2-dimethyl-6-oxo-6*H*-1,3-dioxin-5-yl)-3-(2-thienyl)propanimidothioate (IIIa).** Cyanothioacetamide (**V**), 1.0 g (10 mmol), was dispersed in 25 ml of ethanol, 1.10 ml (10 mmol) of *N*-methylmorpholine was added under stirring, the mixture was stirred for 15 min until it became homogeneous, 2.38 g (10 mmol) of compound **IVa** was added, and the mixture was stirred for 20 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 3.47 g (79%), white powder, mp 140–142°C; published data [1]: mp 139–141°C.

***N*-Methylmorpholinium 2-cyano-3-(4-hydroxy-2,2-dimethyl-6-oxo-6*H*-1,3-dioxin-5-yl)-3-phenylpropanimidothioate (IIIb)** was synthesized in a similar way from 2.32 g (10 mmol) of compound **IVb**. Yield 3.51 g (81%), yellow powder, mp 152–154°C. IR spectrum, ν, cm^{-1}: 1650 (C=O), 2253 (C≡N), 3410 (OH, NH). ^1H NMR spectrum, δ, ppm: 1.39 s (3H, Me), 1.42 s (3H, Me), 2.75 s (3H, NMe), 3.11 m (4H, CH_2NCH_2), 3.78 m (4H, CH_2OCH_2), 4.40 d and 4.61 d (1H, 2-H, J = 12.05 Hz), 5.32 d and 5.48 d (1H, 3-H, J = 12.05 Hz), 6.99–7.21 m (3H, H_{arom}), 7.42–7.54 m (2H, H_{arom}), 9.02 br.s and 9.76 br.s (1H, OH), 9.49 br.s and 9.54 br.s (1H, C=NH); no N^+H signal was observed, presumably due to fast exchange with water present in the solvent. Some signals are doubled, for compound **IIIb** is a mixture of stereoisomers. Found, %: C 57.96; H 6.02; N 9.50. $C_{21}H_{27}N_3O_5S$. Calculated, %: C 58.18; H 6.28; N 9.69.

***N*-Methylmorpholinium 2-cyano-3-(3-ethoxy-4-hydroxyphenyl)-3-(4-hydroxy-2,2-dimethyl-6-oxo-6*H*-1,3-dioxin-5-yl)propanimidothioate (IIIc)** was synthesized in a similar way from 2.93 g (10 mmol) of compound **IVc**. Yield 4.24 g (86%), yellow powder, mp 130–132°C. IR spectrum, ν, cm^{-1}: 1650 (C=O), 2256 (C≡N), 3177–3380 (OH, NH). ^1H NMR spectrum, δ, ppm: 1.23 t (3H, CH_2C**H**$_3$, J = 6.17 Hz), 1.39 s (3H, Me), 1.44 s (3H, Me), 2.62 s (3H, NMe), 2.95 m (4H, CH_2NCH_2), 3.70 m (4H, CH_2OCH_2), 4.08 q (2H, C**H**$_2$CH$_3$, J = 6.17 Hz), 4.22 d and 4.49 d (1H, 2-H, J = 12.14 Hz), 5.25 d and 5.38 d (1H, 3-H, J = 12.14 Hz), 6.48 d and 6.59 d (1H, H_{arom}, J = 6.99 Hz), 6.72 d and 6.95 d (1H, H_{arom}, J = 7.00 Hz), 7.14 s and 7.66 s (1H, H_{arom}), 8.03 br.s (1H, NH), 8.40 br.s (1H, OH), 9.42 br.s and 9.93 br.s (1H, OH). Found, %: C 56.11; H 6.25; N 8.40. $C_{23}H_{31}N_3O_7S$. Calculated, %: C 55.97; H 6.33; N 8.51.

2,2'-Ethylenedisulfanylbis(6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile) (VI) was synthesized as described above for compound **Ia** from 4.33 g (10 mmol) of salt **IIIa** and 0.45 ml (5 mmol) of 1,2-dibromoethane. Yield 3.60 g (74%), white powder, mp 272–274°C (from AcOH). IR spectrum, ν, cm^{-1}: 1680 (C=O), 2184, 2206 (C≡N), 3176 (NH). ^1H NMR spectrum, δ, ppm: 2.62–2.71 m (2H, 5-H), 2.93–3.04 m (2H, 5-H), 3.22–3.38 m (4H, SCH_2), 4.03 t (2H, 4-H, J = 6.90 Hz), 7.23–7.40 m (10H, H_{arom}), 10.62 br.s (2H, 2NH). Mass spectrum, m/z (I_{rel}, %): 489 (5) $[M + 2]^+$, 488 (21) $[M + 1]^+$, 487 (100) $[M]^+$, 257 (33), 138 (12), 111 (8), 99 (13). Found, %: C 64.00; H 4.31; N 11.42. $C_{26}H_{22}N_4O_2S_2$. Calculated, %: C 64.18; H 4.56; N 11.51.

The IR spectra were recorded on an IKS-40 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured in DMSO-d_6 on a Varian Mercury-400 instrument (400.397 MHz) using TMS as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Hewlett–Packard 5890/5972 GC–MS system (HP-5MS column; samples were injected as solutions in methylene chloride). The melting points were determined on a Kofler melting

point apparatus. The progress of reactions was monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

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