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An Expeditious Synthesis of New 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methylpyridine-2(1H)-thiones and Derivatives

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Abstract: A convergent synthesis of 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methylpyridine-2(1H)-thiones and their derivatives S-alkylthiopyridines was described. The main steps towards the formation of the title compounds involve the reactions of 4-alkyloxybenzaldehydes with 2-cyanothioacetamide to afford 2-cyano-3-(4'-alkyloxyphenyl)prop-2-enethioamides which then reacted with acetylacetone prior to the alkylation to give the final compounds 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methyl-2-S-alkylthiopyridines in satisfactory yields.

Key words: 4-alkyloxybenzaldehydes · 2-cyanothioacetamide · 2-cyano-3-(4'-alkyloxyphenyl)prop-2-enethioamides · pyridine-2(1H)-thiones · S-alkylthiopyridine

INTRODUCTION

The interest in the synthesis of new pyridine derivatives prompted us to launch a study on the synthesis of S-alkylthiopyridines. It is common that pyridine-based compounds possess remarkable properties as those reported in the herbicides [1], bactericides [2], fungicides [3] and pharmaceuticals [4-6]. In view of the remarkable biological effects associated to pyridines [7-9], efforts to continue study on the new molecular structures of these compounds remain even up to now.

The impetus towards generating the pyridine-containing compounds can also be ascribed to recently reported pyridine derivatives which showed strong cytotoxicity against several human cancer cell lines [10-13]. In view of these reports and as a continuation of our previous work [14-20] in this area, we are prompted to synthesize some new pyridines and S-alkylthiopyridine derivatives.

Experimental: All the melting points were measured by a Gallenkamp melting point apparatus. The IR spectra for all compounds were recorded on Perkin Elmer System 2000 wherein the samples embedded in KBr pellets. ^{1}H NMR spectroscopic technique was performed by a Bruker 400-MHz Ultrashield ^{TM}FT-NMR spectrometer using $CDCl_3$ as solvent. The CHN microanalysis was carried out using a Perkin Elmer 2400 LS Series CHN/O analyzer. The ESI-TOF-MS measurements were performed on micro TOF II mass spectrometer (Bruker Daltonics) by using acetonitrile as the solvent.

Synthesis of 4-octyloxybenzaldehyde **(1a):** 1-Bromooctane (10.6 g, 0.055 mol) was added to a mixture containing 4-hydroxybenzaldehyde (6.0 g, 0.05 mol) and anhydrous potassium carbonate (15.0 g) in acetone (50 ml). The mixture was refluxed at 62-65°C for 50 h whereupon the inorganic salts obtained were filtered off. The filtrate thus obtained was concentrated under reduced pressure which afforded light yellow oil. Yield: 75%. IR (KBr) (ν/cm^{-1}): 2927, 2856 (CH, aliphatic), 2734 (CH, aldehyde), 1694 (C=O), 1259 (C-O). ^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, J= 6.8 Hz, 3H, CH_3), 1.30-162 (m, 10H, $5CH_2$), 1.82-190 (m, 2H, OCH_2CH_2-$(CH_2)_5$-) 4.08 (t, J= 6.6 Hz, 2H, OCH_2CH_2-), 7.03 (d, J= 8.7 Hz, 2H, ArH), 7.85 (d, J= 2H, 8.7 Hz, 2H, ArH), 9.89 (s, 1H, CHO).

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***4-undecyloxybenzaldehyde* (1b):** The compound **1b** was prepared with the same method as that described for the synthesis of **1a**. Yield: 69%. IR (KBr) (ν/cm^{-1}): 2924, 2852 (CH aliphatic), 2733 (CH aldehyde), 1696 (C=O aldehyde), 1252 (C-O). ^{1}H NMR ($CDCl_3$, δ ppm): 0.89 (t, J= 6.7 Hz, 3H, CH_3), 1.20-1.48 (m, 16H, $8CH_2$), 1.85-190 (m, 2H, OCH_2CH_2-$(CH_2)_8$), 4.05 (t, J= 6.5 Hz, 2H, OCH_2CH_2-), 7.01 (d, J= 8.8 Hz, 2H, ArH), 7.84 (d, J= 8.8 Hz, 2H, ArH), 9.86 (s, 1H, CHO).

***2-Cyano-3-(4'-alkyloxyphenyl)prop-2-enethioamide* (2a, 2b):** To a mixture of cyanothioacetamide (0.02 mol) and the respective 0.02 mol 4-alkoxybenzaldehydes (**1a** and **1b**) in absolute ethanol, a few drops of triethylamine were added. The reaction mixture was heated with stirring at 40-50°C for 30 min and then left to room temperature whereupon the precipitate thus formed was collected by filtration, washed with ethanol and recrystallized from ethanol to give pale yellow crystals of **2a** and **2b**.

***Physical and Analytical Data for 2-cyano-3-(4'-octyloxyphenyl)prop-2-enethioamide* (2a):** Yield 70%. m.p.: 126-127°C; IR (KBr) (ν/cm^{-1}): 3385, 3271, 3178 (NH_2), 2923, 2853 (CH aliphatic), 2219 (CN), 1608 (CH=C), 1267 (C-O). ^{1}H NMR ($CDCl_3$, δ ppm): 0.91 (t, J= 6.8 Hz, 3H, CH_3), 1.28-1.55 (m, 10H, $5CH_2$), 1.80-190 (m, 2H, OCH_2CH_2-$(CH_2)_5$-), 4.09 (t, J= 6.5 Hz, 2H, OCH_2CH_2-), 7.03 (d, J= 9 Hz, 2H, ArH), 7.45 (s br., 1H, NH_2 thioamide), 7.61 (s, br., 1H, NH_2 thioamide), 8.02 (d, J= 9 Hz, 2H, ArH), 8.75 (s, 1H, PhCH=C). Anal. calcd. for $C_{18}H_{24}N_2OS$ (316.46): C, 68.32; H, 7.64; N, 8.85%. Found: C, 68.13; H, 7.59; N, 8.98%.

***Physical and Analytical Data for 2-cyano-3-(4'-undecyloxyphenyl)prop-2-enethioamide* (2b):** Yield 78%. m.p.: 130-131°C; IR (KBr) (ν/cm^{-1}): 3385, 3267, 3178 (NH_2), 2921, 2852 (CH aliphatic), 2220 (CN), 1608 (CH=C), 1266 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, J= 6.7 Hz, 3H, CH_3), 1.22-154 (m, 16H, $8CH_2$), 1.77-190 (m, 2H, OCH_2CH_2-$(CH_2)_8$-), 4.07 (t, J= 6.5 Hz, 2H, OCH_2CH_2-), 7.00 (d, J= 8.9 Hz, 2H, ArH), 7.49 (s, br., 1H, NH_2 thioamide), 7.63 (s, br., 1H, NH_2 thioamide), 8.15 (d, J= 8.9 Hz, 2H, ArH), 8.75 (s, 1H, Ph-CH=C); ESI-TOF-MS: m/z 358.21(M^+), 359.21(M^++1), 360.21(M^++2). Anal. calcd. for $C_{21}H_{30}N_2OS$ (358.54): C, 70.35; H, 8.43; N, 7.81%. Found: C, 70.23; H, 8.39; N, 8.03%.

***Synthesis of 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methylpyridine-2(1H)-thiones* (3a and 3b):** A solution of acetylacetone (1 g, 0.01 mol) and compounds **2a** (0.01 mol) in absolute ethanol (40 ml) containing a few drops of piperidine was refluxed for 4 h. The solid thus obtained were filtered off and recrystallized from ethanol to give yellow needles of **3a.** The same procedure was carried out on compound **2b** which gave yellow needles of **3b** after crystallization with ethanol.

***Physical and analytical data for 5-acetyl-3-cyano-6-methyl-4-(4'-octyloxyphenyl)pyridine-2(1H)-thione* (3a):** Yield 52%. m.p.: 154-155°C; IR (KBr) (ν/cm^{-1}): 3172 (NH), 2933, 2849 (CH aliphatic), 2223 (CN), 1698 ($COCH_3$); ^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (t, J= 6.8 Hz, 3H, CH_3), 1.31-1.51 (m, 10H, $5CH_2$), 1.76-2.00 (m, 2H, OCH_2CH_2-$(CH_2)_5$-), 1.92 (s, 3H, CH_3 at C6), 2.50 (s, 3H, $COCH_3$), 4.02 (t, J= 6.5 Hz, 2H, OCH_2CH_2-), 7.04 (d, J= 8.7 Hz, 2H, ArH), 7.33 (d, J= 8.7 Hz, 2H, ArH), 12.89 (br., 1H, NH pyridine); ESI-TOF-MS: m/z 396.19(M^+), 397.19(M^++1), 398.19(M^++2). Anal. calcd. for $C_{23}H_{28}N_2O_2S$ (396.55): C, 69.66; H, 7.12; N, 7.06%. Found: C, 69.89; H, 7.28; N, 6.99%.

***Physical and analytical data for 5-acetyl-3-cyano-6-methyl-4-(4'-undecyloxyphenyl)pyridine-2-(1H)-thione* (3b):** Yield 55%. m.p.: 173-174°C; IR (KBr) (ν/cm^{-1}): 3172 (NH), 2915, 2849 (CH aliphatic), 2222 (CN), 1698 ($COCH_3$); ^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, J= 6.8 Hz, 3H, CH_3), 1.25-151 (m, 16H, $8CH_2$), 1.79 (s, 3H, CH_3 at C6), 1.80-1.89 (m, 2H, OCH_2CH_2-$(CH_2)_8$-), 2.52 (s, 3H, $COCH_3$), 4.02 (t, J= 6.5 Hz, 2H, OCH_2CH_2-), 7.03 (d, J= 8.8 Hz, 2H, ArH), 7.35 (d, J= 8.8 Hz, 2H, ArH), 13.00 (br., 1H, NH pyridine); ESI-TOF-MS: m/z 438.23(M^+), 439.24(M^++1), 440.23(M^++2), 441.24(M^++3). Anal. calcd. for $C_{26}H_{34}N_2O_2S$ (438.63): C, 71.19; H, 7.81; N, 6.39%. Found: C, 71.10; H, 7.69; N, 6.27%.

***Synthesis of 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methyl-2-S-alkylthio-pyridines* (4a and 4b)**

Method A: To a solution of compound **3a** and **3b** (0.01mol) in dry acetone (40 ml), anhydrous potassium carbonate (0.01 mmol) and 1-bromoalkane (0.01 mmol) were added. The reaction mixture was heated for 2 hrs. with stirring at the temperature 100-120°C. Upon cooling, the salt was filtered off and washed with acetone (30 ml). The total filtrate was concentrated under vacuum and the residue treated with water. The separated white solid was filtered, dried in air and recrystallized from ethanol to give colourless crystals of **4a** and **4b**.

***Physical and analytical data of 5-acetyl-3-cyano-6-methyl-4-(4'-octyloxyphenyl)-2-undecylthiopyridine* (4a):** Yield 72%. m.p.: 60-61°C; IR (KBr) (ν/cm^{-1}): 2919, 2851 (CH aliphatic), 2226 (CN), 1690 ($COCH_3$);

^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, J= 6.7 Hz, 3H, CH_3), 0.91 (t, J= 6.7 Hz, 3H, CH_3), 1.28-159 (m, 26H, $13CH_2$), 1.74-1.86 (m, 4H, SCH_2CH_2 & OCH_2CH_2), 1.89 (s, 3H, CH_3 at C6), 2.53 (s, 3H, $COCH_3$), 3.30 (t, J= 7.3 Hz, 2H, SCH_2CH_2-), 4.00 (t, J= 6.4 Hz, 2H, OCH_2CH_2-), 7.00 (d, J= 8.8 Hz, 2H, ArH), 7.30 (d, J= 8.8 Hz, 2H, ArH); ESI-TOF-MS: m/z 550.41(M^+), 551.41(M^++1), 525.41(M^++2). Anal. calcd. for $C_{34}H_{50}N_2O_2S$ (550.84): C, 74.13; H, 9.15; N, 5.09%. Found: C, 74.38; H, 9.22; N, 4.97%.

***Physical and analytical data of 5-acetyl-3-cyano-6-methyl-2-octylthio-4-(4'-ndecyloxyphenyl)pyridine* (4b):** Yield 80%. m.p.: 78-79°C. IR (KBr) (ν_{max} cm^{-1}): 2923, 2853 (CH aliphatic); 2223 (CN); 1697 ($COCH_3$); ^{1}H NMR ($CDCl_3$, δ ppm): 0.90 (t, J= 6.9 Hz, 3H, CH_3), 0.91 (t, J= 6.9 Hz, 3H, CH_3), 1.25-153 (m, 26H, $13CH_2$), 1.71-1.88 (m, 4H, SCH_2CH_2 & OCH_2CH_2),1.89 (s, 3H, CH_3 at C6), 2.54 (s, 3H, $COCH_3$), 3.30 (t, J= 7.4 Hz, 2H, SCH_2CH_2-), 4.00 (t, 2H, J= 6.5 Hz, OCH_2CH_2-), 7.00 (d, J= 8.8 Hz, 2H, ArH), 7.30 (d, J= 8.8 Hz, 2H, ArH); ESI-TOF-MS: m/z 550.36(M^+), 551.36(M^++1), 525.36(M^++2). Anal. calcd. for $C_{34}H_{50}N_2O_2S$ (550.84): C, 74.13; H, 9.15; N, 5.09%. Found: C, 73.98; H, 8.97; N, 5.25%.

Method B: A mixture containing respective **3a** and **3b** (0.01 mol) in the presence of slight excess of $CH_3CO_2Na.3H_2O$ (1.36 g, 0.01 mol) in ethanol (50 ml) was heated under reflux for 2 hrs. Upon cooling, the colourless precipitate thus formed was collected and recrystallized from ethanol to give compounds **4a** and **4b** in 85 and 88% yields, respectively. These products were identical in all aspects with those obtained from method A.

RESULTS AND DISCUSSION

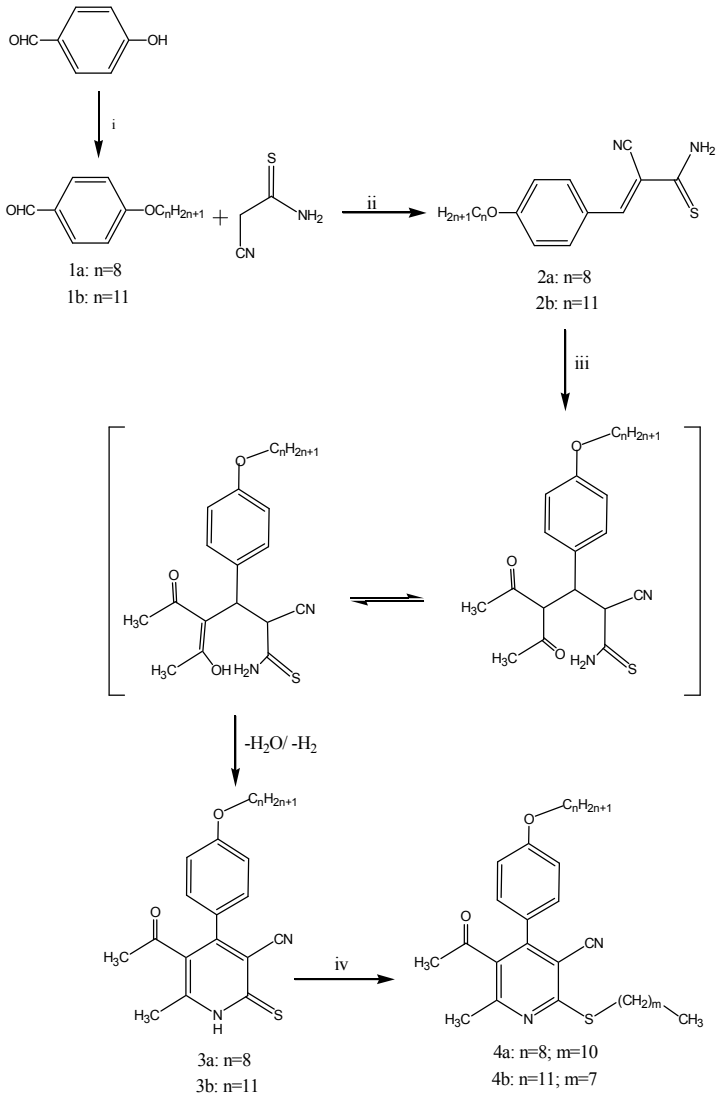
The present study focuses on the synthesis of penta-substituted pyridines and related S-alkylthiopyridines as new compounds which possess biological and medicinal activities. Alkoxybenzaldehydes (**1a** and **1b** in which the alkyl group is C_nH_{2n+1} where n = 8 and 11) were obtained from the Williamson ether reaction between 1-bromoalkane and 4-hydroxybenzaldehyde in the presence of potassium carbonate. It has been found that compounds **1a** and **1b** reacted with 2-cyanothioacetamide to afford 2-cyano-3-(4'-alkyloxyphenyl)prop-2-enethioamides (**2a** and **2b**) which reacted subsequently with acetylacetone in boiling ethanol containing a catalytic amount of piperidine to give yellow crystalline products. The structure of these products was proposed as 5-acetyl-4-(4'-alkyloxyphenyl)-3-cyano-6-methylpyridine-2(1H)-thiones (**3a** and **3b**). The pathway for the conversion from compounds **2** to **3** involved a Michael addition of acetylacetone upon the activated double bond of **2** to give intermediates which in turn underwent several steps encompassing enolization, cyclodehydration and spontaneous dehydrogenation (Scheme 1) leading to compound **3**.

Alkylation of pyridine-3-cyano-2(1H)-thiones (**3a** and **3b**) by bromoalkanes in the presence of potassium carbonate or sodium acetate led to the formation of 5-acetyl-4-(4'-alkyloxyphenyl)-2-alkylthio-3-cyano-6-methylpyridines (**4a** and **4b**). The success of this synthesis can be attributed to the nucleophilicity of S-atom of the SH group.

The structures of the synthesized compounds were characterized by elemental analyses, FTIR and ^{1}H NMR along with ESI-TOF-MS measurement. The percentages of C, H and N from the elemental analysis are in agreement with the theoretical formulation.

The IR spectrum of compound **3a** exhibits a band at 3172 cm^{-1} due to NH group. The absorption bands at 2933 and 2849 cm^{-1} can be assigned to the aliphatic C-H bond. The CN group gives rise to a band with medium intensity at 2223 cm^{-1}. A strong band is observed at 1698 cm^{-1} which can be attributed to the presence of acetyl group. Compounds **3b**, **4a** and **4b** exhibit similar characteristic bands as discussed for **3a**.

The ^{1}H-NMR data for compound **3a** shows a triplet at δ = 0.92 for methyl proton (CH_3) and a multiplet at δ = 1.31-1.51 ppm which can be ascribed to the methylene protons [-O-CH_2-CH_2-$(CH_2)_5$-CH_3]. Whilst the multiplet at δ = 1.76-2.00 ppm is assigned to the methylene [-O-CH_2-CH_2-$(CH_2)_5$-CH_3], the singlets observed at δ = 1.92 ppm and δ= 2.50 ppm are attributed to the CH_3 at C6 pyridine and CH_3 acetyl group, respectively [20]. A triplet at δ= 4.02 ppm attributed to -OCH_2 protons of the alkyloxy chain. Moreover, compound **3a** shows a resonance at δ= 7.04 ppm (d, 2H) and 7.33 (d, 2H) which can be ascribed to the aromatic protons and a broad signal at δ= 12.98 ppm due to NH group. In terms of splitting and chemical shift, the spectra of compounds **3b**, **4a** and **4b** are similar to that of compound **3a.** However, it is important to note that in the spectra of compounds **4a** and **4b** an additional triplet is observed at δ= 3.30 ppm owing to the presence of -SCH_2 protons and the absence of a broad signal of NH group. The mass spectra of the title compounds show the molecular ion peaks which are in agreement with their molecular formula.



Scheme 1: Synthetic route for the formation of title compounds

Reagents: (i) BrC_nH_{2n+1}, K_2CO_3, acetone; (ii) Et_3N, EtOH; (iii) acetylacetone, piperidine, EtOH; (iv) BrC_mH_{2m+1}, K_2CO_3, acetone or BrC_mH_{2m+1}, AcOONa, EtOH

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