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ORIGINAL ARTICLE

Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their insecticidal activity

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Abstract The work included in this paper involves the synthesis of thirteen heterocyclic compounds, piperidinium and morpholinium 3-cyanopyridinethiolates **5–14**, **17**, **20** and **21** in our Lab. and their characterization using elemental and spectroscopic analyses. The insecticidal activities of these compounds against cowpea aphid, *Aphis craccivora* using acetamiprid insecticide as a reference were studied. The bioassay results showed that: (i) the insecticidal activities of compounds **13**, **14** and **20** against nymphs or adults of cowpea aphid are about 1.5-fold higher than that of acetamiprid after 48 h of treatment, (ii) the rest of the tested compounds (ten compounds) exhibit weak to strong toxicity against cowpea aphid and (iii) there is a remarkable relationship between the structure and activity of the tested compounds.

1. Introduction

In recent years, pyridine-containing neonicotinoids have been the fastest-growing and most important class for the insecticide market [1], with widespread use against a broad spectrum of sucking and certain chewing insects by acting selectivity on insect nicotinic acetylcholine receptors (*n*AChRs), their molecular target site [2–5]. Pyridine-containing neonicotinoids are reported to possess a relatively low risk for non-target organisms and the environment, high target specificity and versatile application methods [5]. The common molecular structural features of neonicotinoids consist of four sections: (i) aromatic heterocycle, (ii) flexible linkage, (iii) hydroheterocyle or guanidine/amidine and (iv) electron-withdrawing segment [6]. Encouraged by the above findings and as a continuation of our programme directed towards the synthesis of new pyridine-containing heterocycles with anticipated insecticidal activities [7], we undertook the synthesis of the title compounds, which contain the aforementioned main structural

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features of neonicotinoids and studying their insecticidal activities against Cowpea aphid, *Aphis craccivora* hoping to get compounds with more potency, low insect resistance and no environmental pollution.

2. Experimental section

2.1. General

Melting points of all compounds were determined on Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N, and S) were conducted using a Vario EL C, H, N, S Analyzer. The IR spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer using KBr disc technique (ν_{max} in cm^{-1}). ^1H NMR Spectra were recorded on a Bruker 400 MHz spectrometer with chemical shifts given in δ (ppm) and coupling constant (J) given in Hz. using *TMS* as internal reference. Mass spectra were recorded on a Jeol JMS-600 mass spectrometer. The purity of the synthesized compounds was checked by TLC. Key intermediates **1a–d** [8], **2a,b** [9] and **3a,b** [10] were prepared in our laboratory according to the reported methods. Neonicotinoid insecticide, (*E*)-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methylacetamidine (acetamiprid, purity >98%) was purchased from Sigma–Aldrich chemicals (France). Field strain of cowpea aphids, *A. craccivora* were collected from faba bean, *Vicia faba,* fields of Assiut University Experimental Farm during 2014/2015 season.

Compounds **5**–**14**, **17**, **20** and **21** as well as acetamiprid were tested against nymphs and adults of cowpea aphids, *A. craccivora*.

2.2. Synthetic procedure for 3-cyano-5-ethoxycarbonyl-6-methyl-4-styrylpyridine-2(1H)-thione (2c)

To a mixture of β-styryl-α-thiocarbamoylacrylonitrile (**1c**) (2.14 g, 10 mmol) and ethyl acetoacetate (1.3 ml, 10 mmol) in ethanol (25 ml), a few drops of triethylamine were added. The resulting mixture was heated under reflux for 4 h and then acidified with drops of glacial acetic acid. The product that formed after cooling was collected by filtration and recrystallized from ethanol to give yellow crystals of **2c**. Yield: 53%. Melting point (mp): 260–262 °C. IR (ν) (KBr) cm^{-1}: 3200 (NH), 2220 (CN), 1730 (CO). ^1H NMR (CF_3CO_2D) δ: 7.35–7.60 (m, 7H, CH═CH and Ar—H), 4.30–4.52 (q, 2H, OCH_2), 2.63 (s, 3H, CH_3), 1.25–1.40 (t, 3H, CH_3). Elemental Analysis Calculated for $C_{18}H_{16}N_2O_2S$ (%): C, 66.65; H, 4.97; N, 8.64; S, 9.88. Found (%): C, 66.44; H, 4.77; N, 8.91; S, 10.15.

2.3. Synthetic procedure for 5-acetyl-3-cyano-6-methyl-4-(2′-thienyl)pyridine-2(1H)-thione (4)

To a mixture of β-(2′-thienyl)-α-thiocarbamoylacrylonitrile (**1d**) (2.09 g, 10 mmol) and acetylacetone (1.0 mL, 10 mmol) in ethanol (25 ml), a few drops of triethylamine were added. The resulting mixture was heated under reflux for 4 h and then acidified with a few drops of glacial acetic acid. The product that formed after cooling was collected by filtration and recrystallized from ethanol to give yellow crystals of **4**. Yield: 78%. mp: 273–275 °C. IR (ν) (KBr) cm^{-1}: 3200 (NH), 2220 (CN), 1700 (CO). ^1H NMR ($CDCl_3$) δ: 13.02 (s 1H, NH), 7.55 (s, 1H, CH thienyl), 7.26 (s, 1H, CH thienyl), 7.10 (s, 1H, CH thienyl), 2.41 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{14}H_{13}N_2OS_2$ (%): C, 58.11; H, 4.53; N, 9.68; S, 22.16. Found (%): C, 58.09; H, 4.43; N, 9.28; S, 22.00.

2.4. General procedure for the reaction of β-aryl-α-thiocarbamoylacrylonitrile (1a or 1b) with 5,5-dimethylcyclohexane-1,3-dione; formation of morpholinium salts 13 and 14

To a suspension of β-aryl-α-thiocarbamoylacrylonitrile (**1a** or **1b**) (10 mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1.4 g, 10 mmol) in ethanol (15 ml), 0.9 ml (10 mmol) of morpholine was added. The reaction mixture was heated under reflux for 6 h and then allowed to cool. The precipitated solid was filtered off and recrystallized from ethanol as yellow crystals of compounds **13** or **14**.

2.4.1. Morpholinium 3-cyano-7,7-dimethyl-4-(4′-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-2-thiolate (13)

Yield: 53%. mp: 208–210 °C. IR (ν) (KBr), cm^{-1}: 3440, 3279 (NH, N^+H_2), 2947 (C—H, aliphatic), 2173 (CN), 1619 (CO); ^1H NMR (DMSO-d_6) δ: 8.70 (br s, 2H, N^+H_2); 8.32 (s, 1H, NH), 7.01–7.03 (d, J = 8.0 Hz, 2H, Ar—H), 6.74–6.76 (d, J = 8.0 Hz, 2H, Ar—H), 4.20 (s, 1H, $C_{(4)}H$), 3.74–3.76 (t, J = 4.0 Hz, 4H, CH_2OCH_2), 3.69 (s, 3H, OCH_3), 3.08–3.10 (t, J = 4.0 Hz, 4H, $CH_2N^+CH_2$), 2.31 (s, 2H, CH_2 at C-8), 2.06–211 (d, J = 20.0 Hz 1H, $C_{(6)}H$), 1.89–1.93 (d, J = 16.0 Hz, 1H, $C_{(6)}H$), 0.98 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{23}H_{29}N_3O_3S$ (%): C, 64.61; H, 6.84; N, 9.83; S, 7.50: Found (%): C, 64.54; H, 6.61; N, 9.77; S, 7.19.

2.4.2. Morpholinium 4-(4′-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquino-line-2-thiolate (14)

Yield: 55%. mp: 207–209 °C. IR (ν) (KBr), cm^{-1}: 3420 (N^+H_2), 3278 (NH), 2948 (C—H, aliphatic), 2172 (CN), 1606 (CO); ^1H NMR (DMSO-d_6): 8.65 (br. s, 2H, N^+H_2); 8.42 (s, 1H, NH), 7.24–7.26 (d, J = 8.0 Hz, 2H, Ar—H), 7.10–7.12 (d, J = 8.0 Hz, 2H, Ar—H), 4.26 (s, 1H, $C_{(4)}H$), 3.75–3.77 (t, J = 4.0 Hz, 4H, CH_2OCH_2), 3.09–3.12 (t, J = 4.0 Hz, 4H, $CH_2N^+CH_2$), 2.32 (s, 2H, CH_2 at C-8), 2.08–2.11 (d, J = 12.0 Hz, 1H, $C_{(6)}H$), 1.90–1.94 (d, J = 16.0 Hz, 1H, $C_{(6)}H$), 0.98 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{22}H_{26}ClN_3O_2S$ (%): C, 61.17; H, 6.07; N, 9.73; S, 7.42. Found (%): C, 61.25; H, 6.21; N, 9.52; S, 7.49.

2.5. Synthetic procedure for 4-(4′-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexa-hydroquinoline-2-thiol (15)

An aqueous solution of compound **14** (2.0 g) in 30 ml distilled water was acidified with diluted HCl (10 %). The solid product was collected by filtration and crystallized from ethanol to give compound **15** as fine white needles. Yield: 93%. mp: 271–272 °C. IR (ν) (KBr), cm^{-1}: 3220 (NH), 2239 (CN), 1622 (CO). ^1H NMR ($CDCl_3$): 11.83 (s, 1H, SH), 8.86 (s, 1H, NH), 6.87–6.89 (d, J = 8.0 Hz, 2H, Ar—H), 6.77–6.79 (d, J = 8.0 Hz, 2H, Ar—H), 4.19 (s, 1H, $C_{(4)}H$), 2.33 (s, 2H,