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Synthesis and spectral characterization of selective pyridine compounds as bioactive agents

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Starting from 3-cyano-4,6-distyrylpyridin-2(1*H*)-thione (1), the compound *N*-(4-chlorophenyl)-2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2) was prepared. Compound (2) underwent cyclization upon heating in ethanolic sodium ethoxide solution to give the corresponding cyclized form 3-amino-*N*-(4-chlorophenyl)-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (3). The elemental analyses and spectroscopic data of compounds (2) and (3) are in agreement with their proposed structures. Their insecticidal activity against cowpea aphid, *Aphis craccivora* Koch, was studied. The results of insecticidal activity for compounds (2) and (3) against the nymphs and the adults of the tested insects exhibited that compounds (2) and (3) have a higher insecticidal activity than that of acetamiprid, a reference insecticide, after 24 h of treatment.

1. Introduction

The chemistry of functionalised pyridine compounds has been extensively developed, which is reflected in many papers that have been published.[1-8] This is associated with both a theoretical interest in this class of organic compounds and a very broad spectrum of the practical uses of pyridine derivatives. For example, more than 10% of the most commonly used modern medicines contain pyridine or the hydrogenated pyridine ring.[9]

A lot of neonicotinoids insecticides contain pyridine ring in their structure and at the present time the use of these insecticides is increased in the field of crop protection as a result of their different advantages.[10-15] As an Expanding our work that focused on the synthesis of heterocyclic compounds and continuing our investigations on the chemistry of some pyridine derivatives neonicotinoid analogs,[1-6] we report herein the synthesis of two new heterocyclic compounds containing pyridine ring

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and screened their insecticidal activity against cowpea aphid, *Aphis craccivora* Koch (Homoptera: Aphididae) in the presence of acetamiprid insecticide as a reference.

2. Results and Discussion

2.1 Chemistry

Compounds **2** and **3** were synthesized here as a result of the well known biological activity of the compounds containing pyridine moiety. Reaction of compound (**1**) "3-cyano-4,6-distyrylpyridin-2(1*H*)-thione", which was prepared according to the reported method,[6] with 2-chloro-*N*-(4-chlorophenyl)acetamide in ethanol containing slightly excess amounts of fused sodium acetate for 30 min afforded the compound 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (**2**). The chemical structure of compound **2** was confirmed by elemental and spectral analysis. Compound **2** underwent intramolecular *Thorpe-Ziegler* cyclization upon heating in ethanol containing catalytic amounts of sodium ethoxide for 5 min to give the corresponding cyclized form 3-Amino-*N*-(4-chlorophenyl)-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (**3**) (see **Fig. 1**). Spectroscopic data and elemental analyses of compound **3** were in agreement with its proposed structure.

IR spectrum of compound **2** showed absorption bands at 3292, 2216 and 1662 cm^{-1} characteristics for (NH), (C≡N) and (C=O) groups respectively. The absorption band of (C≡N) of compound **2** was disappeared when cyclised to give the thienopyridine **3** and was replaced by 3462 and 3408 cm^{-1} for NH_2. ^1H NMR spectrum (DMSO-d_6, 400 MHz) of compound **2** showed singlet signals at 10.51 and 4.27 for (NH) and (CH_2) groups respectively. The signal of (CH_2) group of compound **2** was disappeared when cyclised to give compound **3**. DEPT 135 (DMSO-d_6, 100 MHz) spectrum of compound **2** showed characteristic signal at 35.36 for (CH_2) group which disappeared when cyclised to give compound **3**.

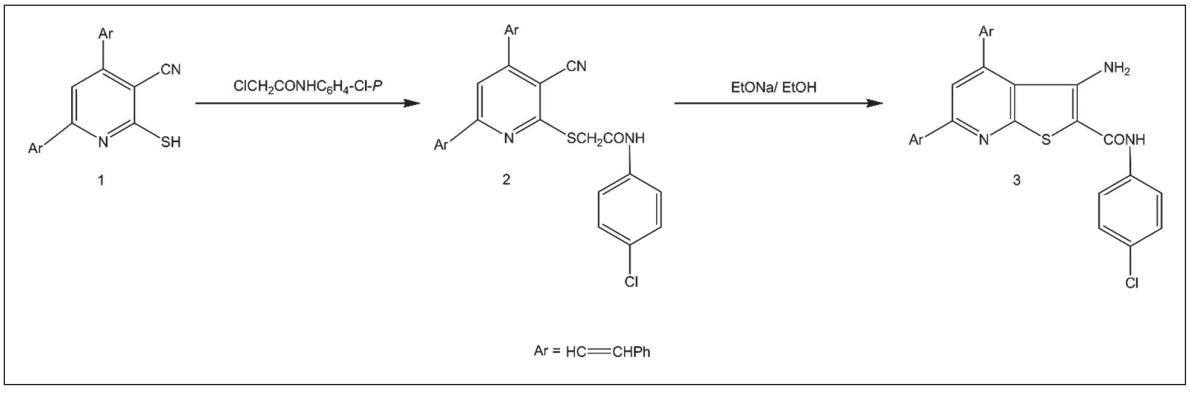

Fig. 1. Synthesis of compounds **2** and **3**.

*2.2 Insecticidal activity of compounds **2** and **3**.*

2.2.1 Insecticidal activity test for the cowpea aphid nymphs.

Compounds **2** and **3** were tested for their insecticidal activity against the nymphs of the collected aphids and the results are presented in **Table 1**. After 24 h, insecticidal activity data showed that compounds **2** and **3** exhibited strong to weak insecticidal activity against nymphs of cowpea aphid and the LC_{50} values were 0.029 and 0.040 ppm, respectively, whereas the LC_{50} value of acetamiprid was 0.045 ppm. After 48 h of test, it is found that the insecticidal activity of compounds **2** and **3** against nymphs of cowpea aphid, *Aphis craccivora* Koch ranged from good to moderate and LC_{50} values were 0.006 and 0.007 ppm, respectively, whilst the LC_{50} value of acetamiprid 0.006 ppm. These results indicate that compounds **2** and **3** have excellent insecticidal activity compared with the insecticidal

activity of acetamiprid insecticide because the toxic ratio of compounds **2** and **3** is more than that of acetamiprid after 24 h of test.

Table 1. Insecticidal activity of acetamiprid and compounds **2** and **3** against the cowpea aphid nymphs after 24 and 48 h of treatment.

	24 h after treatment			48 h after treatment		
Compd	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**
Acetamiprid	0.34±0.02	0.045	1	0.42±0.03	0.006	1
2	0.41±0.03	0.029	1.552	0.49±0.04	0.006	1
3	0.40±0.03	0.040	1.125	0.47±0.04	0.007	0.857

Notes: toxic ratio is defined as the ratio of acetamiprid's LC_{50} value for baseline toxicity and the compound's LC_{50} value.

2.2.2 Insecticidal activity test for the cowpea aphid adults

Compounds **2** and **3** were tested for their insecticidal activity against the adults of the gathered aphids and the results are in **Table 2**. The results showed that after 24 h of test, compounds **2** and **3** have strong to weak activity and LC_{50} values were 0.149 and 0.183 ppm, respectively, whilst the LC_{50} value of acetamiprid was 0.225 ppm. After 48 h of insecticidal activity test, the insecticidal activity of compounds **2** and **3** varied from high to low and LC_{50} values were 0.017 and 0.022 ppm, respectively, against cowpea aphid adults, whilst 0.023 ppm was the LC_{50} value of acetamiprid. The above results revealed that the insecticidal activity of compounds **2** and **3** against adults of cowpea aphid was more than that of acetamiprid after 24 and 48 h of treatment.

Table 2. Insecticidal activity of acetamiprid and compounds **2** and **3** against the cowpea aphid adults after 24 and 48 h of treatment

	24 h after treatment			48 h after treatment		
Compd	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**
Acetamiprid	0.24±0.02	0.225	1	0.32±0.03	0.023	1
2	0.36±0.03	0.149	1.510	0.38±0.03	0.017	1.353
3	0.36±0.03	0.183	1.229	0.40±0.03	0.022	1.045

Notes: toxic ratio is defined as the ratio of acetamiprid's LC_{50} value for baseline toxicity and the compound's LC_{50} value.

2.2.3 Structure-action relationship

According to the general framework structure of the used compounds **2** and **3**, it appears that the compound *N*-(4-chlorophenyl)-2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2) is more active than the compound 3-amino-*N*-(4-chlorophenyl)-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (3) against the cowpea aphids. The high activity associated with compound **2** may be due to the presence of the opened form structure in compound **2** and the presence of cyano group, but compound **3** was found in the cyclized form and cyano group is absent in its structure.

3. Conclusion

In this work, two heterocyclic compounds namely, *N*-(4-chlorophenyl)-2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2) and 3-amino-*N*-(4-chlorophenyl)-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (3), have been prepared in pure state and their insecticidal activity against cowpea aphid, *Aphis craccivora* Koch was evaluated. The results of this insecticidal activity illustrated that these compounds have a higher activity against cowpea aphid than that of acetamiprid insecticide and this emphasizes the importance of pyridine compounds in the agricultural uses.

4. Experimental

4.1 Materials and methods

Melting points were determined by using a Fisher-Johns apparatus for the compounds **2** and **3**. Elemental analysis (C, H, N, and S) was determined by a Vario EL C, H, N, S analyzer. DEPT 135, ^{1}H NMR and ^{13}C NMR spectra measurement were accomplished via a Bruker 400 MHz spectrometer in the presence of tetramethylsilane (TMS) as an internal reference. Infrared (IR) spectra were determined by a Pye-Unicam SP3-100 spectrophotometer using the KBr disk technique. Thin-layer chromatography (TLC) was used for the purity check of the synthesized compounds and δ (ppm) is the unit of chemical shifts. The field strain of cowpea aphids was collected from faba bean, *Vicia faba* L., fields of the experimental farm of Assiut University. Compound **1** was prepared according to the reported method[6] and the acetamiprid insecticide was purchased from Sigma-Aldrich (France). Acetamiprid insecticide and compounds (**2** and **3)** were tested against the collected cowpea aphid, *Aphis craccivora* Koch.

4.2 Synthetic procedure for N-(4-chlorophenyl)-2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2).

A mixture of compound **(1)** (2 g, 0.006 mol), 2-chloro-*N*-(4-chlorophenyl)acetamide (1.2 g, 0.006 mol), and fused sodium acetate (0.6 g, 0.007 mol) in ethanol (25 mL) was heated under reflux for 30 min. The formed precipitate was collected and recrystallized from ethanol-dioxane mixture (1:2) as Pale orange crystals of compound **2**. Yield: 85%. m. p. 224- 225°C. IR (ν) (KBr) cm^{-1}: 3292 (NH), 2921 (C-H aliphatic), 2216 (C≡N), 1662 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.51 (s, 1H, NH), 7.21-7.84 (m, 19H, 2CH=CH and Ar-H), 4.27 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.83, 162.01, 157.37, 155.81, 149.56, 136.17, 135.70, 132.78, 130.77, 129.54, 129.26, 128.04, 127.88, 126.89, 122.21, 115.42, 114.65, 114.39, 101.83, 35.36. DEPT 135 (DMSO-d_6, 100 MHz): δ 135.70 (CH), 132.78 (CH), 129.54 (CH), 129.26 (CH), 128.04 (CH), 127.88 (CH), 126.87 (CH), 122.23 (CH), 114.65 (CH), 113.39 (CH), 35.36 (CH_2). Elemental Analysis Calculated for $C_{30}H_{22}ClN_3OS$ (%): C, 70.92; H, 4.36; N, 8.27; S, 6.31. Found (%): C, 70.95; H, 4.41; N, 8.25; S, 6.33.

4.3 Synthetic procedure for 3-Amino-N-(4-chlorophenyl)-4,6-distyrylthieno[2,3-b]pyridine-2-carboxamide (3).

Compound **(2)** (2.5 g, 0.005 mol) were suspended in sodium ethoxide solution (0.5 g of sodium in 31 mL of absolute ethanol) and heated for 5 min under reflux. The formed product after cooling was collected and recrystallized from ethanol-dioxane mixture (1:2) as orange crystals of compound **3**. Yield: 89%. m. p. 243- 244°C. IR (ν) (KBr) cm^{-1}: 3462, 3408, 3326 (NH, NH_2), 3025 (C-H aromatic), 2921, 2850 (C-H aliphatic), 1647 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.61 (s, 1H, NH), 6.96-8.04 (m, 21H, 2CH=CH, NH_2 and Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.53, 158.01, 155.37, 144.67, 136.98, 136.27, 134.34, 133.18, 133.08, 129.28, 128.09, 127.73, 123.76, 123.67, 122.69, 122.37, 121.99, 121.79, 117.58. DEPT 135 (DMSO-d_6, 100 MHz): δ134.33 (CH), 133.18 (CH), 129.28 (CH), 123.75 (CH), 123.67 (CH), 122.69 (CH), 122.37 (CH), 121.99 (CH), 121.79 (CH), 117.58 (CH).

Elemental Analysis Calculated for $C_{30}H_{22}ClN_3OS$ (%): C, 70.92; H, 4.36; N, 8.27; S, 6.31. Found (%): C, 70.94; H, 4.35; N, 8.31; S, 6.32.

4.4 Laboratory bioassay

The insecticidal activity for the aforementioned compounds **2** and **3** was checked via leaf dip bioassay method.[16] The concentration of these chemical compounds that is required to kill 50% (LC_{50}) of cowpea aphid, *Aphis craccivora* Koch was reported here. In this experiment, six concentrations of compounds **2** and **3** plus 0.1% Triton X-100 as a surfactant were used and a total of 20 adults and 20 nymphs, approximately of the same size, were dipped for 10 seconds in each concentration three times. The treated aphids were allowed to dry at room temperature for about 0.5 h. Control batches of aphids were similarly dipped in a solution of distilled water plus 0.1% Triton X-100. Then, after drying of the treated batches of cowpea aphids, they were transferred to Petri dishes (9 cm diameter) and held for 24 and 48 h at 22 + 2 °C, 60 + 5% relative humidity, and photoperiod of 12:12 (light/dark). Recording aphid mortality was 24 and 48 h after treatment by using a binocular microscope. The aphid that was unable to coordinate forward movement was considered dead. Insecticidal activity test of compounds **2** and **3** was repeated twice and the results were corrected using Abbott's formula.[17] Median lethal concentrations (LC_{50}) and slope values of compounds **2** and **3** were determined by the Probit regression analysis program and expressed in parts per million (ppm).[18]

References

1. Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2014**) Pyridine derivatives as insecticides. Part 1: Synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, Aphis craccivora Koch (Homoptera: Aphididae). *J. Agric. Food Chem.*, 62 (41) 9982–9986.
2. Bakhite E. A., Abd-Ella A. A., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2017**) Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their Insecticidal Activity. *J. Saud. Chem. Soc.*, 21 (1) 95–104.
3. Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., Zaki R. M., and Abdel-Raheem Sh. A. A. (**2019**) Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents. *Toxicol. Rep.*, 6 100-104.
4. Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., and Abd-Ella A. A. (**2021**) Synthesis and characterization of some distyryl-derivatives for agricultural uses. *Eur. Chem. Bull.*, 10 (1) 35-38.
5. Abdel-Raheem Sh. A. A., Kamal El-Dean A. M., Hassanien R., El-Sayed M. E. A., and Abd-Ella A. A. (**2020**) Synthesis and biological activity of 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide and its cyclized form. *Alger. j. biosciences*, 01 (02) 046-050.
6. Kamal El-Dean A. M., Abd-Ella A. A., Hassanien R., El-Sayed M. E. A., and Abdel-Raheem Sh. A. A. (**2019**) Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New Pyridine Derivatives. *ACS Omega*, 4 (5) 8406-8412.
7. Zaki R. M., Kamal El-Dean A. M., Mickey J. A., Marzouk N. A., and Ahmed R. H. (**2017**) Synthesis, reactions, and antioxidant activity of 3-(pyrrol-1-yl)-4,6-dimethyl selenolo[2,3-*b*]pyridine derivatives. *Synth. Commun.*, 47 (24) 2406-2416.
8. Altaf A. A., Shahzad A., Gul Z., Rasool N., Badshah A., Lal B., and Khan E. A (**2015**) Review on the Medicinal Importance of Pyridine Derivatives. *J. Drug Des. Med. Chem.*, 1 (1) 1-11.
9. Lukevits É. (**1995**) Pyridine derivatives in the drug arsenal (150 years of pyridine chemistry). *Chem. Heterocycl. Compd*., 31 (6) 639–650.
10. Zhang N., Tomizawa M., and Casida J. E. (**2004**) α-Nitro Ketone as an Electrophile and Nucleophile: Synthesis of 3-Substituted 2-Nitromethylenetetrahydrothiophene and tetrahydrofuran as Drosophila Nicotinic Receptor Probes. *J. Org. Chem.*, 69 (3) 876-881.

11. Shimomura M., Yokota M., Ihara M., Akamatsu M., Sattelle D. B., and Matsuda K. (**2006**) Role in the Selectivity of Neonicotinoids of Insect-Specific Basic Residues in Loop D of the Nicotinic Acetylcholine Receptor Agonist Binding Site. *Mol. Pharmacol.*, 70 (4) 1255–1263.
12. Tomizawa M., and Casida J. E. (**2003**) Selective toxicity of neonicotinoids attributable to specificity of insect and mammalian nicotinic receptors. *Annu. Rev. Entomol.*, 48 339–364.
13. Tomizawa M., Talley T., Maltby D., Durkin K. A., Medzihradszky K. F., Burlingame A. L., Taylor P., and Casida J. E. (**2007**) Mapping the elusive neonicotinoid binding site. *Proc. Natl. Acad. Sci. U.S.A.*, 104 (21) 9075–9080.
14. Kagabu S., Ishihara R., Nishimura K., and Naruse Y. (**2007**) Insecticidal and neuroblocking potencies of variants of the imidazolidine moiety of imidacloprid-related neonicotinoids and the relationship to partition coefficient and charge density on the pharmacophore. *J. Agric. Food Chem.*, 55 (3) 812–818.
15. Yang Z. B., Hu D. Y., Zeng S., and Song B. A. (**2016**) Novel hydrazone derivatives containing pyridine amide moiety: Design, synthesis, and insecticidal activity. *Bioorg. Med. Chem. Lett.*, 26 (4) 1161-1164.
16. O'Brien P. J., Abdel-Aal Y. A., Ottea J. A., and Graves J. B. (**1992**) Relationship of insecticide resistance to carboxylesterases in *Aphis gossypii* (Homoptera: Aphididae) from Midsouth cotton. *J. Econ. Entomol.*, 85 (3) 651–657.
17. Abbott W. S. (**1925**) A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.*, 18 (2) 265–267.
18. Finney D. J. (**1952**) *Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve*, 2nd Ed, Cambridge Univ. Press, Cambridge, U. K.