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FACILE SYNTHESIS AND PESTICIDAL ACTIVITY OF SUBSTITUTED HETEROCYCLIC PYRIDINE COMPOUNDS

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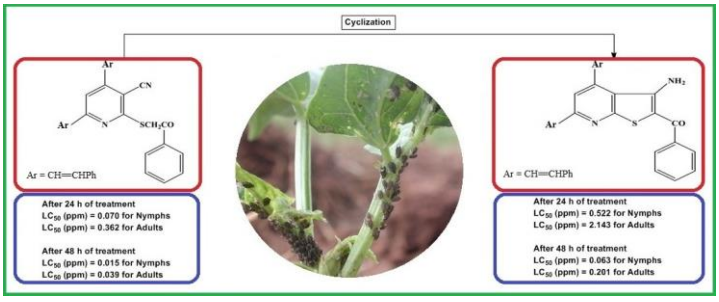
2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetophenone **(2)** was synthesized by the reaction of 3-cyano-4,6-distyrylpyridin-2(1*H*)-thione **(1)** with an alkylating agent, phenacyl bromide in the presence of fused sodium acetate and ethanol. Compound **2** underwent *Thorpe-Ziegler* cyclization upon heating in ethanolic sodium ethoxide solution to yield the target, 3-amino-2-benzoyl-4,6-distyrylthieno[2,3-*b*]pyridine **(3)**. Elemental and spectral characterizations of the newly synthesized compounds **2** and **3** have been achieved. Both compounds **2** and **3** exhibited significant insecticidal activities after treated for 24 and 48 h compared with the reference compound, acetamiprid, when screened for their insecticidal activity against the nymphs and adults of cowpea aphid, *Aphis craccivora* Koch. Therefore, the results obtained are very promising, and accentuate on the importance of such heterocyclic pyridine compounds as efficient pesticides.



INTRODUCTION

Pyridine, a heterocyclic nucleus, has attracted a wide-ranging attention for the chemist in search for the novel therapeutic agents. As a result of the various pharmacological applications of this ring,[1-3] several researchers are recently engaged in the improvement of pharmacologically active agents bearing it. Modern improvements made by researchers in this manner are documented.[4-6]

Owing to the remarkable applications of pyridine in the agricultural field, incorporation of pyridine moiety with the further heterocycles to form polycyclic structures with an additional functional variety, is progressively becoming a fruitful scope of the study for their appreciable biological activity.

Motivated with the above findings associated with our ongoing attention in the field of pyridine and other heterocycles as insecticidal agents,[7-29] the present work was devoted to synthesize new substituted compounds bearing pyridine and thieno[2,3-*b*]pyridine ring, and examine their insecticidal activity.

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RESULTS AND DISCUSSION

1. Chemistry

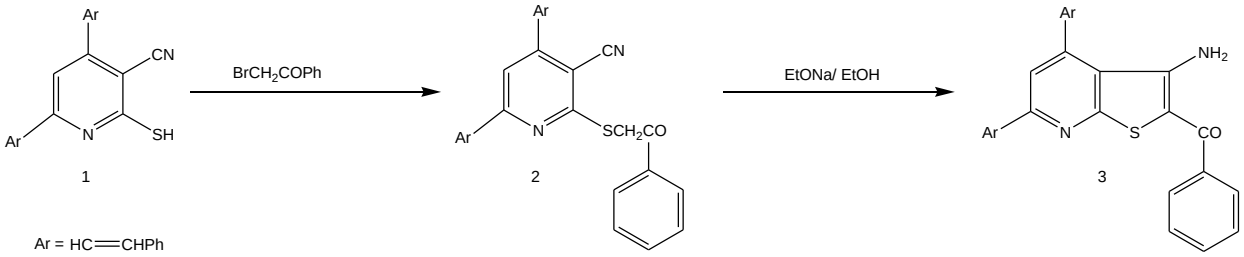
The synthetic strategy of the target compounds **2** and **3** starting from compound **1** is described in Scheme 1. The basic intermediate **1** which was prepared according to the reported method,[12] reacts with phencyl bromide in ethanol containing fused sodium acetate for 30 min yielding the corresponding *S*-alkylated derivative **2**. The chemical structure of compound **2** was established by elemental and spectral analysis. Compound **2** then underwent intramolecular Thorpe-Ziegler cyclization upon refluxing in ethanol containing catalytic amounts of sodium ethoxide for 5 min to give the corresponding thienopyridine derivative **3** (see Scheme 1). The structure of compound **3** is in a agreement with the testified data.

IR spectrum of compound **2** showed absorption bands at 2210 and 1700 cm^{-1} assigned to (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**, which was turned to 3475 and 3276 cm^{-1} characteristic to NH_2 group. The ^1H NMR spectrum (DMSO-d_6, 400 MHz) of compound **2** showed singlet at 4.17 for (CH_2) group, which was thereafter disappeared upon cyclization to compound **3**. DEPT 135 (DMSO-d_6, 100 MHz) spectrum of compound **2** showed characteristic signal at 38.23 assigned to (CH_2) group, which disappeared when cyclised to give compound **3**.

2. Insecticidal activity of compounds 2 and 3

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 cowpea aphids and the results are clearly presented in Table 1. After the treatment for 24 h, compounds **2** and **3** showed a strong to weak insecticidal activity against nymphs of cowpea aphid with estimate LC_{50} values of 0.070 and 0.522 ppm, respectively, whereas the LC_{50} value of acetamiprid was 0.045 ppm. After the treatment for 48 h, it was found that the insecticidal activity of compounds **2** and **3** varies from a good to moderate with LC_{50} values of 0.015 and 0.063 ppm, respectively, while that of acetamiprid was found to be 0.006 ppm. These results indicate that compounds **2** and **3** have a good insecticidal activity in comparison with acetamiprid insecticide as clearly evident from the LC_{50} values measured after 24 and 48 h of treatment.



Scheme 1 – Synthesis of compounds **2** and **3**.

Table 1

Insecticidal activity of compounds **2** and **3** against the cowpea aphid nymphs after **24** and **48** h of treatment in comparison with acetamiprid

	24 h after treatment			48 h after treatment		
Compound	**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	0.44±0.03	0.070	0.643	0.47±0.03	0.015	0.400
3	0.38±0.02	0.522	0.086	0.45±0.03	0.063	0.095

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

Table 2

Insecticidal activity of compounds **2** and **3** against the cowpea aphid adults after **24** and **48** h of treatment in comparison with acetamiprid

	24 h after treatment			48 h after treatment		
Compound	**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±0.02	0.362	0.622	0.41±0.03	0.039	0.589
3	0.36±0.02	2.143	0.105	0.43±0.02	0.201	0.114

* The 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. 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 summarized in Table 2. The results showed that after 24 h of treatment, compounds **2** and **3** have a strong to weak activity with estimate LC_{50} values of 0.362 and 2.143 ppm, respectively, while the LC_{50} value of acetamiprid was found to be 0.225 ppm. After treated for 48 h, the insecticidal activity of compounds **2** and **3** varied from a high to low against cowpea aphid adults and LC_{50} values were 0.039 and 0.201 ppm, respectively, whereas the LC_{50} value of acetamiprid was 0.023 ppm. The above results revealed that the insecticidal activity of compounds **2** and **3** against adults of cowpea aphid was close to that of acetamiprid after 24 and 48 h of treatment.

2.3. Structure-action relationship

According to the general frame structure of the investigated compounds **2** and **3**, it appears that the corresponding *S*-alkylated derivative **2** is more active than thienopyridine derivative **3** against the cowpea aphids. The high activity associated with compound **2** may be due to the presence of the opened form structure of 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.

EXPERIMENTAL

1. Materials and methods

Melting points were uncorrected and determined by using a Fisher-Johns apparatus. Elemental analyses were determined by a Vario EL C, H, N, S analyzer. Infrared (IR) spectra were determined by a Pye-Unicam SP3-100 spectrophotometer using the KBr disk technique. DEPT 135, ^{1}H NMR and ^{13}C NMR spectra measurements were accomplished via a Bruker 400 MHz spectrometer in the presence of tetramethylsilane (TMS) as an internal reference, δ (ppm) is the unit of chemical shifts. Thin-layer chromatography (TLC) technique was used for the purity check of the synthesized compounds. 3-cyano-4,6-distyrylpyridin-2(1*H*)-thione **(1)** was prepared according to the literature procedure,[12] and the acetamiprid insecticide was purchased from Sigma-Aldrich (France). Insecticidal activity of synthesized compounds against cowpea aphid, *Aphis craccivora* Koch (Homoptera: Aphididae) was achieved using acetamiprid as a reference insecticide.

2. Synthetic procedure for 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetophenone (2)

An equimolar mixture of compound **(1)** (2 g, 0.006 mol), phenacyl bromide (0.006 mol) was refluxed in ethanol (25 mL) containing fused sodium acetate (0.6 g, 0.007 mol) for 30 min. The formed precipitate was collected and recrystallized from ethanol-dioxane mixture (1:2) as Pale-yellow crystals of compound **2**. Yield 87%; m. p. 197- 198°C; FT-IR (KBr, Cm^{-1}): 3021 (C-H aromatic), 2917 (C-H aliphatic), 2210 (C≡N), 1700 (C=O), 1633 (C=N); ^{1}H NMR δ (400 MHz, DMSO-d_6, ppm): δ 7.07-8.18 (20H, m, 2CH=CH and Ar-H), 4.17 (2H, s, CH_2); ^{13}C NMR (100 MHz DMSO-d_6, ppm): δ 193.26, 161.70, 157.03, 149.66, 138.71, 136.53, 134.02, 130.34, 129.58, 129.22, 128.85, 128.10, 127.69, 126.48, 122.07, 115.63, 114.63, 101.88, 38.23; DEPT 135 (100 MHz DMSO-d_6, ppm): δ 138.71 (CH), 136.53 (CH), 134.02 (CH), 130.34 (CH), 129.68 (CH), 129.22 (CH), 128.85 (CH), 128.10 (CH), 127.69 (CH), 126.47 (CH), 122.07 (CH), 114.63 (CH), 38.23 (CH_2); Anal. Calcd for: $C_{30}H_{22}N_2OS$: C, 78.57; H, 4.84; N, 6.11; S, 6.99; Found: C, 78.56; H, 4.82; N, 6.12; S, 6.98.

3. Synthetic procedure for 3-amino-2-benzoyl-4,6-distyrylthieno[2,3-*b*]pyridine (3)

Compound **(2)** (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 91%; m. p. 272- 273°C. FT-IR (KBr, Cm^{-1}): 3475, 3276 (NH_2), 3056, 3027 (C-H aromatic), 2917, 2848 (C-H aliphatic), 1632 (C=O); ^{1}H NMR δ (400 MHz, DMSO-d_6,

ppm): δ 6.83-8.34 (22H, m, 2CH=CH, NH_2 and Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 189.44, 162.73, 156.88, 152.27, 147.90, 142.54, 141.35, 136.30, 135.57, 131.55, 129.59, 129.43, 129.23, 128.91, 127.95, 127.82, 127.56, 122.05, 118.97, 103.61; DEPT 135 (100 MHz DMSO-d_6, ppm): δ 135.57 (CH), 131.55 (CH), 129.61 (CH), 129.43 (CH), 129.23 (CH), 128.91 (CH), 128.03 (CH), 127.95 (CH), 127.81 (CH), 127.56 (CH), 127.04 (CH), 118.97 (CH); Anal. Calcd for: $C_{30}H_{22}N_2OS$ (%): C, 78.57; H, 4.84; N, 6.11; S, 6.99. Found: C, 78.55; H, 4.88; N, 6.12; S, 6.97.

4. Laboratory bioassay

The insecticidal activity for the tested compounds **2** and **3** was checked via leaf dip bioassay method.[30] The concentration of these chemical compounds that is required to kill 50% (LC_{50}) of cowpea aphids was reported here. In this testing, 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 permitted to dry at room temperature for about 0.5 h. Control batches of aphids were likewise dipped in a solution of distilled water plus 0.1% Triton X-100. Then, after dehydrating 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 unable of coordinated forward movement was considered dead. Insecticidal activity test of compounds **2** and **3** was frequented twice and the results were corrected using Abbott's formula.[31] 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).[32]

CONCLUSION

In this work, two derivatives namely, 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)acetophenone **(2)** and 3-amino-2-benzoyl-4,6-distyrylthieno[2,3-*b*] pyridine **(3)** were synthesized and their insecticidal activity were evaluated as well. The bioassay results demonstrated that these compounds have good activity against cowpea aphid compared with that of acetamiprid insecticide and this emphasize the significance of pyridine compounds in different fields.

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