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The thiazoylmethoxy modification on pyrazole oximes: Synthesis and insecticidal biological evaluation beyond acaricidal activity

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ABSTRACT

A series of new pyrazole oximes bearing substituted thiazole ring were designed and prepared. The structures of the title compounds were identified by spectral analyses. The results of primary bioassay indicated that some targeted compounds exhibited promising insecticidal activity besides acaricidal activity, particularly; compounds **8c** and **8d** were more potent against *Tetranychus cinnabarinus* and *Plutella xylostella* than other analogues.

1. Introduction

During the past two decades, different classes of pyrazole oxime compounds have been investigated and many of them are found to possess broad spectrum of bioactivities such as fungicidal [1–3], acaricidal [4], insecticidal [5], anti-TMV [6,7], antibacterial [8], and anti-inflammatory activities [9]. For example, fenpyroximate (in Fig. 1), a well-known agricultural acaricide bearing a pyrazole oxime moiety in the structure, has been reported to exhibit strong acaricidal activity against several phytophagous mites on diverse crops [10]. As a result, pyrazole oxime containing heterocycles became a focus of chemical and pharmaceutical research.

Moreover, thiazole derivatives due to their unique chemical and structural properties have drawn much attention recently and are widely used in the fields of pesticides and medicines. Some thiazole compounds were also synthesized as potential insecticides [11,12] and fungicides [13]. Some thiazole-containing derivatives also showed plant growth regulatory [14], herbicidal [15], antimicrobial [16], and anti-inflammatory [17] activities. Recently, Wang et al. [18] reported that some 2-cyanoacrylate compounds carrying a benzenyloxy-linked thiazole unit displayed good bioactivities. This gave a great impetus to the search for biologically active molecules bearing substituted thiazole group.

Inspired by these facts, we envisioned that the introduction of the highly substituted thiazole moiety to the parent pyrazole oxime scaffold might afford some new compounds (Fig. 1) possessing wide spectrum bioactivities such as acaricidal and insecticidal activity. We report herein the synthesis and biological evaluation of a variety of novel pyrazole oximes carrying substituted thiazole unit.

2. Experimental

The synthetic route for the targeted compounds is shown in Scheme 1. Starting from 2-chloro-5-chloromethylthiazole **1**, intermediates **2**, **3**, **4** were prepared in good yields according to the reported protocols [18]. Intermediate **5** was conveniently obtained by a similar method in the literature [19]. The intermediate aldehyde **6** was successively synthesized *via* the reaction of the corresponding aldehyde **5** with the respective substituted phenols or 2-naphthalenol [19,20]. Compound **6** was further converted to the oxime **7** by a reaction with hydroxylamine hydrochloride using potassium hydroxide as a base. Finally, treatment of oxime **7** with the key intermediate **4** under basic conditions afforded the desired compounds **8a**–**8o** in satisfactory yields. Optimized reaction conditions were adopted to synthesize a class of new pyrazole oxime derivatives containing substituted thiazole moiety. Their biological activity against *Tetranychus cinnabarinus* and *Plutella xylostella* was evaluated according to the method described in literature [21–23].

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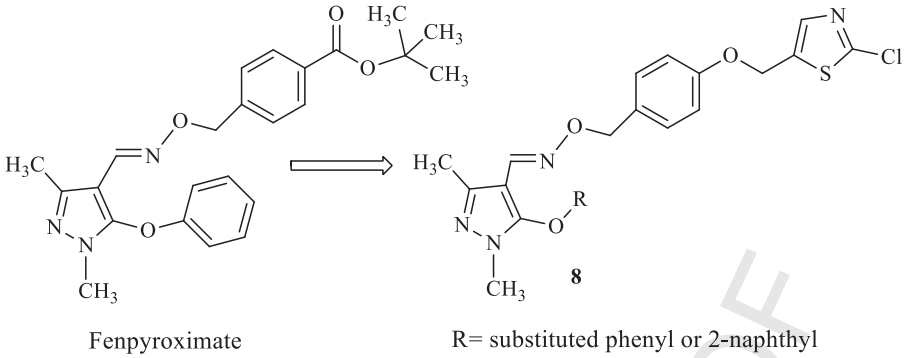
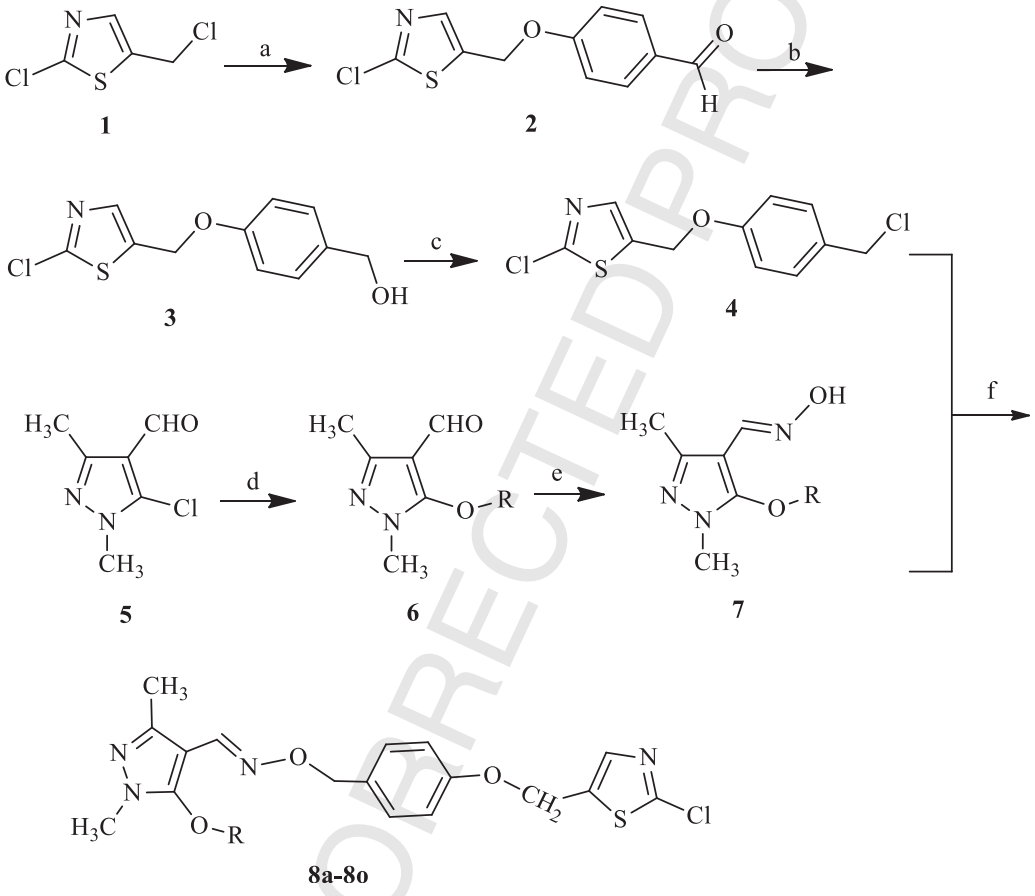


Fig. 1. Strategic design of the title compounds.



Scheme 1. Reagents and conditions: (a) p-hydroxybenzaldehyde, potassium carbonate, ethanol, reflux for 8 h; (b) $NaBH_4$ (2.0 equiv.), ethanol, 0 °C for 1 h, r.t. for 2 h; (c) thionyl chloride (1.5 equiv.), dichloromethane, 0 °C for 30 min, r.t. for 12 h; (d) substituted phenols or 2-naphthalenol, potassium hydroxide, DMF, 40 °C for 2 h, 110 °C for 4–12 h; (e) hydroxylamine hydrochloride, potassium hydroxide, methanol, reflux for 6–12 h; (f) potassium carbonate, acetonitrile, reflux for 8–24 h.

3. Results and discussion

All the final derivatives **8a–8o** were purified by column chromatography on silica gel with the solvent system of ethyl acetate and petroleum ether (60–90 °C), and their structures were fully identified by ^{1}H NMR, ^{13}C NMR and elemental analysis. The details are given in Supporting information. The ^{1}H NMR spectrum of **8a** showed a singlet peak at δ 2.37 attributed to the methyl protons at the 3-position of the pyrazole ring. A singlet at δ 3.58 is due to the methyl protons at the 1-position of the pyrazole ring. Two singlets appeared in 5.14 and 4.93 ppm are due to the two methylene protons in the molecule. The presence of two singlet signals at δ 7.51 and 7.78 are assignable to thiazole-4-CH and CH=N protons, respectively. In the ^{13}C NMR spectrum of **8a**, the peak belonging to CH=N group is observed at δ 152.7. The biological activity data are listed in Table 1. Fenpyroximate was used as a positive control. As shown in Table 1, some designed compounds displayed promising acaricidal activity against *T. cinnabarinus* at a concentration of 200 μg/mL. For example, compounds **8c**, **8d**, and **8i** achieved around 90% inhibition against *T. cinnabarinus*, which was comparable to that of the control Fenpyroximate. Additionally, compounds **8c**, **8d**, **8i** and **8j** showed moderate to good inhibition against *T. cinnabarinus* when the dosage was reduced to 100 μg/mL. Encouragingly, some of the designed compounds were also active against *P. xylostella* at the concentration of 200 μg/mL. Among them, compounds **8b**, **8c**, **8d**,

Table 1
Acaricidal and insecticidal activities of compounds **8a–8o** (mortality, %).

Compounds	R	*T. cinnabarinus*		*P. xylostella*	
		200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
8a	Phenyl	0	–	33	0
8b	3-Fluorophenyl	0	–	86	71
8c	4-Fluorophenyl	95	80	100	57
8d	4-Chlorophenyl	90	80	100	71
8e	2-Bromophenyl	0	–	0	–
8f	4-Bromophenyl	50	0	71	0
8g	3-Nitrophenyl	0	–	32	0
8h	2-Methylphenyl	0	–	27	0
8i	3-Methylphenyl	90	70	86	43
8j	4-Methylphenyl	80	50	57	0
8k	4-Tert-butylphenyl	0	–	0	–
8l	6-Chloro-3-methylphenyl	0	–	0	–
8m	2,3-Dimethylphenyl	0	–	0	–
8n	2,4-Difluorophenyl	0	–	0	–
8o	2-Naphthyl	0	–	0	–
Fenpyroximate		100	100	–	–

"–" refers to "not tested".

and **8i** displayed good to excellent insecticidal activity against *P. xylostella* with inhibitory values of 86, 100, 100, and 86%, respectively. Moreover, compounds **8b**, **8c**, and **8d** had moderate insecticidal activity against *P. xylostella* at the dosage of 100 μg/mL. The data presented in Table 1 also showed that 4-fluoro substituted compound **8c** and 4-chloro substituted analogue **8d** were more potent against *T. cinnabarinus* and *P. xylostella* than other oxime derivatives. All the above data indicated that the biological activity spectrums of pyrazole oxime derivatives were significantly improved *via* the introduction of the substituted thiazole moiety. These studies represent an important basis for the development of novel pesticides in future.

4. Conclusion

In summary, we have achieved the synthesis of a series of new pyrazole oxime derivatives bearing substituted thiazole moiety. Preliminary bioassay demonstrated that some of the targeted compounds possessed insecticidal property besides acaricidal activity. Particularly, compounds **8c** and **8d** displayed relatively good acaricidal activity against *T. cinnabarinus* and potential insecticidal activity against *P. xylostella* at the testing concentrations. Further structural modifications and bioactivity investigations on these new active compounds are currently in progress.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.06.011.

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