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Note

Reaction of Ketene Dithioacetals with Pyrazolylcarbohydrazide: Synthesis and Biological Activities of Ethyl 5-Amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate†

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The title compound, $C_{16}H_{23}N_5O_3S$, ethyl 5-amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate (**5**) has been synthesized by the treatment of ethyl 2-cyano-3,3-dimethylthioacrylate with 1-*t*-butyl-5-methyl-4-hydrazinocarbonylpyrazole (**4**) in refluxed ethanol. The possible mechanism of the above reaction was also discussed. The results of biological test show that the title compound has fungicidal and plant growth regulation activities.

Keywords pyrazole, ethyl 2-cyano-3,3-dimethylthioacrylate, reaction mechanism, biological activity

Introduction

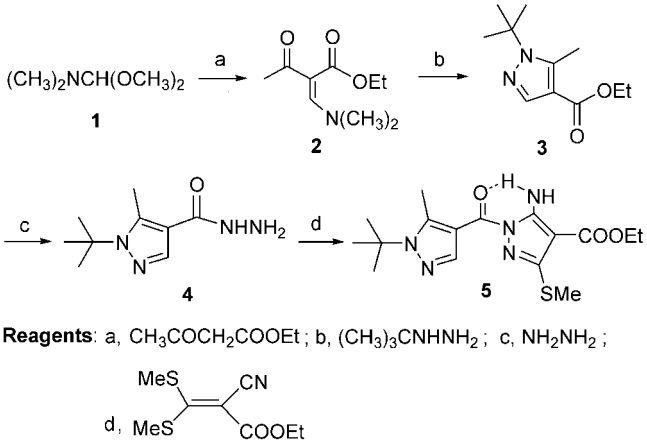
Pyrazole and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities. During the past years, considerable evidence has been accumulated to demonstrate the efficacy of pyrazole derivatives including antibacterial,[1] antifungal,[2] herbicidal,[3] insecticidal[4] and other biological activities.[5-7] Up to now, a great variety of these kind of compounds have been synthesized, among which some commercially pesticides have been developed including fripronil (MB46030),[8] ET-751[9] and pyrazolate (A-544).[10] The synthesis of heterocyclic compounds containing multi-structure in a molecule has received much attention in recent years.[11] However, a survey of the literatures revealed that linked biheterocyclic compounds containing pyrazoles via carbonyl group have seldom been reported. In view of the above mentioned reasons and as a continuation of our research for new and better biologically active agents, we describe herein the synthesis of a novel compound, ethyl 5-amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate (**5**), which was characterized by ^{1}H NMR, IR, elemental and X-ray diffraction analysis. The result of biological test shows that the title compound has fungicidal and plant growth regulation activities.

Experimental

^{1}H NMR spectra ($CDCl_3$) were recorded on a Bruker AC-600 instrument with TMS as an internal standard, and IR spectra were taken on a Nicolet 510P (KBr) spectrometer. The elemental analysis was performed on a Perkin-Elmer 240 analyzer. The melting points were determined on an X-4 microscopic melting point apparatus and uncorrected.

The synthetic route for title compound is outlined in Scheme 1.

Scheme 1 Procedure of preparing the title compound



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The intermediates of **1**, **2**, **3** were synthesized according to references.[12] Compound 5-methyl-1-*t*-butyl-4-hydrazinopyrazole (**4**) was prepared by the reaction of hydrazine hydrate with **3**: A mixture of compound **3** (1.050 g, 0.005 mol) and *t*-butylhydrazine (0.440 g, 0.005 mol) in 15 mL of ethanol was refluxed for 4 h, cooled to room temperature, and filtered. The crude product was recrystallized from ethanol to give new intermediate **4** as white crystal. Yield 77.4%, m.p. 169—171 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 9.18 (s, 1H), 7.73 (s, 1H), 4.28 (s, 2H), 2.68 (s, 3H), 1.57 (s, 9H); IR (KBr) *v*: 3269 (N—H), 1660 (C=O), 1612, 1501 (C=C, C=N) cm^{-1}. Anal. calcd for $C_9H_{16}N_4O$: C 55.06, H 8.22, N 28.56; found C 55.11, H 8.23, N 28.49. The title compound ethyl 5-amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate (**5**) was prepared as follows: A mixture of 5-methyl-1-*t*-butyl-4-hydrazinopyrazole (**4**) (0.006 mol, 1.18 g) and ethyl 2-cyano-3,3-dimethylthioacrylate (0.006 mol, 1.30 g) in 12 mL of ethanol was refluxed for 2 h. The reaction mixture was cooled to room temperature and the separated solid was filtered, washed several times with cold ethanol, dried and recrystallized from ethanol to give ethyl 5-amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate (**5**) as white crystal. Yield 87.2%, m.p. 162—163 ℃; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.49 (s, 1H, CH=N), 4.31 (q, *J*=7.6 Hz, 2H), 2.80 (s, 3H), 2.53 (s, 3H), 1.38 (t, *J*=7.6 Hz, 3H), 1.70 (s, 9H). IR (KBr) *v*: 3478, 3357 (N—H), 1677 (C=O), 1602, 1516 (C=C, C=N) cm^{-1}. Anal. calcd for $C_{16}H_{23}N_5O_3S$: C 52.59, H 6.34, N 19.16; found C 52.74, H 6.23, N 19.02.

Determination of crystal structure

A light yellow crystal of the compound **5** with dimension of 0.24 mm×0.18 mm×0.16 mm was mounted on a glass fiber in a random orientation. The data were collected by BRUKER SMART 1000 CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.071073 nm) using ω scan mode in the range of $1.67° \leqslant \theta \leqslant 26.42°$ at temperature 293(2) K. A total of 10336 reflections were collected with 3749 unique ones (R_{int}=0.0371), of which 2430 reflections with $I > 2\sigma(I)$ were considered to be observed and used in the succeeding refinements. Intensity data were corrected for Lp factors and empirical absorption. The structure was solved by direct methods and expanded by using Fourier differential techniques with SHELXL-97.[13] All non-hydrogen atoms were located with successive difference Fourier syntheses. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added according to the theoretical models. Full matrix least-squares refinement gave the final wR_2=0.0586 and wR=0.1558, $W=1/[\sigma^2(F_o^2) + (0.1014P)^2 + 0.29P]$, where $P=(F_o^2 + 2F_c^2)/3$, S=1.056, $(\Delta/\sigma)_{max}$=0.000 e•Å^{-3}, $(\Delta\rho)_{max}$=0.62 e•Å^{-3}, $(\Delta\rho)_{min}$=−0.26 e•Å^{-3}. Figure 1 shows the molecular structure of the compound. Packing diagram of the compound in a unit cell is shown in Figure 2.

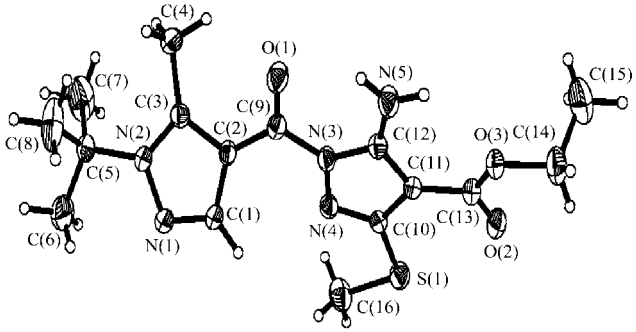


Figure 1 Molecular structure of the title compound.

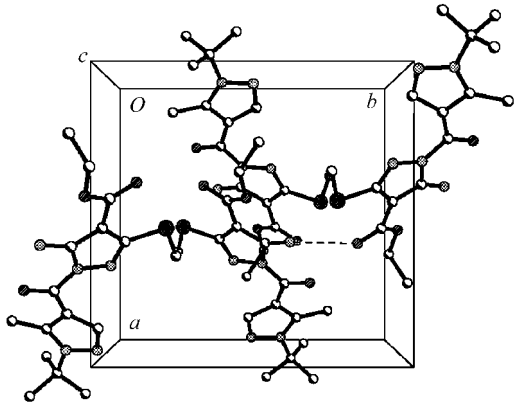
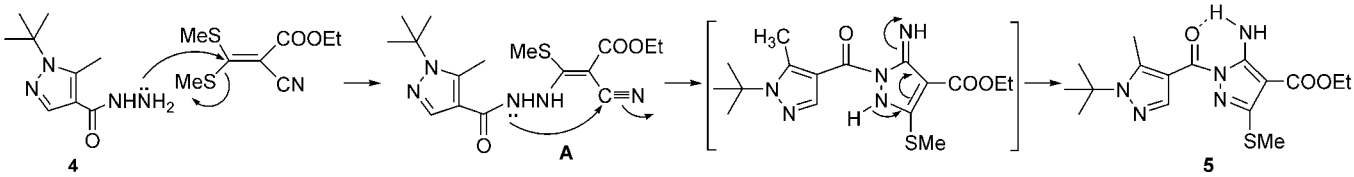


Figure 2 Packing diagram in a unit cell of the title compound.

Results and discussion

Ketene dithioacetals are versatile reagents for the synthesis of pyrazole and pyrimidine derivatives.[14-18] During the course of our studies directed toward exploring the potential of ketene dithioacetals for synthesizing new classes of novel bipyrazole compounds, we found that the synthesis of pyrazole derivatives was obtained by the condensation reaction of ketene dithioacetal with hydrazine derivatives. In the extension of our investigation of ketene dithioacetals, we now wish to report a new one-pot synthesis of polyfunctionalized pyrazole by the reaction of ketene dithioacetal with active hydrazine derivatives containing pyrazole ring. In spite of numerous reactions of ketene dithioacetals with nucleophiles such as amine or active methylene compounds, to the best of our knowledge, the reaction with 5-methyl-1-*t*-butyl-4-hydrazinopyrazolyle has been unknown for the purpose of synthesis of heterocycles. Thus, it has been found that ethyl 2-cyano-3,3-dimethylthioacrylate reacts with 5-methyl-1-*t*-butyl-4-hydrazine pyrazolyle (**4**) in the presence of refluxing ethanol to give the corresponding ethyl 5-amino-1-(5'-methyl-1'-butyl-4'-pyrazolyl)carbonyl-3-methylthio-1*H*-pyrazole-4-carboxylate (**5**) in excellent yield. The structure of the reaction product **5** was established and confirmed by their elemental analysis, spectral data (IR,^{1}H NMR) and X-ray diffraction. The ^{1}H NMR spectrum showed a

Scheme 2 Proposed mechanism of generation of the title compound



singlet at δ 2.80 assigned to a methylthio group, a broad band at δ 8.49 assigned to the CH═N group. The formation of **5** was assumed to proceed via a nucleophilic attack of the NH_2 group to the ethylenic bond in dithioacetals followed by elimination of 1 mole of methyl mercaptan to give the intermediate (**A**), which was followed by intramolecular attack on C≡N by NH, and then underwent cyclization to the final product **5**. The reaction mechanism is shown in Scheme 2.

Biological activity

The preliminary biological test showed that the title compound exhibited inhibiting activity against four fungi, *Gibberrella zeave*, *Alternaria solani*, *Phoma asparagi* and *Cercosporsa arachidicola hori*, but not remarkably. Its inhibiting rates reached 28.6%, 33.3%, 29.4% and 29.4% at 50 μg/mL, respectively. In addition, it also exhibited promoting activity on the production of cucumber cotyledom root, and the promoting rates reached 50.5% at 10 μg/mL. It possesses lower inhibiting activity toward elongation of wheat coleoptile segments, and its inhibiting rates reached −1.8% at 10 μg/mL.

In summary, ethyl 5-amino-1-(5'-methyl-1'-*t*-butyl-4'-pyrazolyl)carbonyl-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (**5**) can be synthesized readily from the cyclization of ethyl 2-cyano-3,3-dimethylthioacrylate with **4** in refluxing ethanol. The present methodology has the advantage of mild condition, good yield and easy manipulation.

References

1 Patel, H. V.; Fernandes, P. S.; Vyas, K. A. *Indian J. Chem.* **1990**, *29B*, 135.
2 Chen, H. S.; Li, Z. M. *Chin. J. Chem.* **2000**, *18*, 596.
3 Morimoto, K. M.; Makino, K.; Yamamoto, S.; Sakato, G. *J. Heterocycl. Chem.* **1990**, *27*, 807.
4 Huang, R. Q.; Song, J.; Feng, L. *Chem. J. Chin. Univ*. **1996**, *17*, 1089.
5 Pande, A.; Saxena, V. K. *Indian J. Chem.* **1987**, *26B*, 390.
6 Gong, P.; Zhao, Y. F.; Wang, D. *Chin. Chem. Lett.* **2002**, *13*, 613.
7 Kopp, M.; Lancelot, J. C.; Dallemagne, P.; Rault, S. *J. Heterocycl. Chem.* **2001**, *38*, 1045.
8 Colliot, F.; Kukorowski, K. A.; Hawkins, D. W.; Roberts, D. A. *Brighton Crop Prot. Conf. —Pests Dis* **1992**, (1), 29.
9 Miura, Y.; Ohnishi, M.; Mabuchi, T.; Yanai, I. *Brighton Crop Prot. Conf. —Weeds* **1993**, (1), 35.
10 Konotsune, T.; Kawakubo, K.; Honma, T. *JP* 8035035, **1980** [*Chem. Abstr*. **1980,** *93*, 20750].
11 Chen, H. S.; Li, Z. M.; Han, Y. F. *J. Agric. Food Chem.* **2000,** *48*, 5312.
12 Menozzi, G. M.; Mosti, L.; Schenone, P. *J. Heterocycl. Chem.* **1987**, *24*, 1669.
13 (a) Sheldrick, G. M. *SHELXS-97, Program for X-ray Crystal Structure Solution*, Göttingen University, Germany, **1997**. (b) Sheldrick, G. M. *SHELXS-97, Program for X-ray Crystal Structure Refinement*, Göttingen University, Germany **1997**.
14 Kohar, S.; Tominaga, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1988**, *25*, 959.
15 Baraldi, P. G.; Francesca, F.; Tabrizi, A. M.; Preti, D.; Romagnoli, R.; El-Kashef, H.; Moorman, A.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2003**, *46*, 1229.
16 Elgemeie, G. E. H.; Elghandour, A. H.; Elzanate, A. M.; Elaziz, G. W. A. *Synth. Commun.* **2003**, *33*, 253.
17 Elgemeie, G. E. H.; Elzanate, A. M.; Elghandour, A. H.; Ahmed, S. A. *Synth. Commun.* **2002**, *33*, 3509.
18 Norton, P. P. *J. Heterocycl. Chem.* **1986**, *23*, 193.

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