Asian Journal of Chemistry; Vol. 26, No. 15 (2014), 4883-4886

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16460

Synthesis, Crystal Structure and Fungicidal Activity of Novel 1,5-Diaryl-3-benzoyloxy-1*H*-pyrazoles

YUAN-YUAN LIU[1,*,†], YI LI[2,*,†], HONG-JUN ZHU[3], KAI CHEN[3], BIN HUANG[1] and YA-PING YANG[1]

[1]Department of Chemical and Pharmaceutical Engineering, Southeast University ChengXian College, Nanjing 210088, P.R. China
[2]College of Biotechnology and Pharmaceutical Engineering, Nanjing University of Technology, Nanjing 210009, P.R. China
[3]Department of Applied Chemistry, College of Science, Nanjing University of Technology, Nanjing 210009, P.R. China

*Corresponding authors: E-mail: liuyuanyuan1985419@163.com; liynj2012@njut.edu.cn
†These authors contribute to this work equally

Received: 1 October 2013; *Accepted*: 17 December 2013; *Published online*: 16 July 2014; AJC-15592

Seven novel 1,5-diaryl-3-benzoyloxy-1*H*-pyrazoles (**2a-2g**) were prepared by the DCC condensation of 1,5-diaryl-1*H*-pyrazol-3-ols (**1a-1g**) with benzoic acid. Their structures were characterized by elemental analysis, IR, ^{1}H NMR and mass spectral data. The structure of 5-(3,4-dimethoxyphenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (**2d**) was also determined by single crystal X-ray diffraction analysis. Bioassay results indicated that the compounds 5-(4-fluorophenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (**2f**) and 1,5-diphenyl-3-benzoyloxy-1*H*-pyrazole (**2a**) exhibited excellent-to-medium fungicidal activity against *Sclerotinia sclerotiorum* at a dosage of 10 μg/mL. The structure-activity relationships (SAR) were also discussed

Keywords: 1,5-Diaryl-3-benzoyloxy-1*H*-pyrazoles, Fungicidal activity, Crystal structure, Structure-activity relationships.

INTRODUCTION

Since the discovery of pyrazole fungicide pyraclostrobin by BASF scientists[1-3], aryl substituted oxypyrazole derivatives have gained enormous attention due to their diverse bioactivities in fungicide[4,5], insecticide[6] and herbicide[7]. We have reported a series of novel 1,5-diaryl-3-oxypyrazoles containing alkyloxy-acetate[8], oxy(2-thioxothiazolidin-3-yl)ethanone[9], or glucopyranosyl moieties[10] with fungicidal activity. On the other hand, several biological studies have also indicated the value of benzoyloxy as bioactive group[11,12]. However, very few bioactive benzoyl substituted 1,5-diaryl-3-oxypyrazole derivatives have *hitherto* been described in the literature.

In this article, the synthesis of a series of novel 1,5-diaryl-3-benzoyloxy-1*H*-pyrazoles (**2a-2g**) and the crystal structure of 5-(3,4-dimethoxyphenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (**2d**) are reported. Meanwhile, their fungicidal activity has been investigated with the aim of understanding the structure-activity relationships (SAR) and developing novel fungicides. A preliminary *in vitro* bioassay indicated that some compounds displayed good fungicidal activity at the dosage of 10 μg/mL.

EXPERIMENTAL

All reagents were analytical grades and solvents were dried by standard methods and distilled before use. 1,5-Diaryl-1*H*-pyrazol-3-ols (**1a-1g**) were prepared from methyl 3-aryl-acrylates according to the reported procedure including addition-cyclization and oxidation[8].

General procedure: Benzoic acid (0.24 g, 2 mmol) was dissolved in a solution of DCC (0.43 g, 2.1 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at 0 °C for 1 h. Then, **1a-1g** (2 mmol) and DMAP (0.02 g, 0.2 mmol) was added. The solution was stirred at 0 °C for 2 h and then kept at room temperature for 12 h. The white precipitate formed was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (50 g) eluting with petroleum ether/ethyl acetate 4:1 to gain the pure product **2a-2g**.

Detection method: Melting points were measured on an X-4 microscope electrothermal apparatus (Taike, China) and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 300 or 500 MHz in $CDCl_3$ or DMSO-d_6, with tetramethylsilane as an internal standard. IR spectra were recorded in KBr disk using a Nicolet 380 FT-IR spectrophotometer. Mass spectra were recorded with an Agilent 1100 Series LC/MSD Trap SL. Elemental analyses were performed on a Flash EA-1112 elemental analyzer.

X-ray crystallography: X-ray crystallographic analysis of **2d** were performed on a Nonius CAD-4 single-crystal diffractometer by using MoK_α radiation (λ = 0.71073 Å) with an $\omega/2\theta$ scan mode at 293 K. The structure was solved by

direct methods and refined by full-matrix least-squares procedures on F^2 using SHELXL-97 program[13]. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were introduced at calculated positions. The isotropic temp. factors were fixed to 1.2 times (1.5 times for CH_3 groups) the equivalent isotropic displacement parameters of the C-atom the H-atom is attached to.

CCDC-906894 contains the supplementary crystallographic data for **2d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 3360-33; e-mail: deposit@ccdc.cam.ac.uk).

Fungicidal assays: The fungicidal activity against *Sclerotinia sclerotiorum*, *Gibberella zeae* and *Rhizoctonia cerealis* was investigated. The fungi were obtained from Jiangsu Pesticide Research Institute Co., Ltd., China. The tested compounds **2a-2g** were dissolved in acetone and added to a sterile agarized *Czapek-Dox* medium at 45 ºC. In preliminary screenings, the compounds were used in a concentration of 10 µg/mL. The control sample contained only one equivalent of acetone. The media were poured onto 8 cm *Petri dishes* (10 mL for each dish) and after 2 days inoculated with 5 mm PDA discs of overgrown mycelium. In the case of *Sclerotinia sclerotiorum*, the medium was inoculated by a prick of laboratory needle containing fungus spores. The Petri dishes were incubated at room temperature in the dark. After 4 days, the diameters of the inoculation of the cultures were measured. The percentage inhibition of fungal growth was determined by comparison between the development of fungi colonies on media containing compounds and on the control. Three replicates of each test were carried out.

1,5-Diphenyl-3-benzoyloxy-1*H*-pyrazole (2a): White crystal, m.p. 110-111 °C, yield 0.68 g (86 %). ^{1}H NMR spectrum (500 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.17 (2H, q, *J* = 1.3, 8.3, Ar-H), 7.80 (1H, t, *J* = 7.5, Ar-H), 7.65 (2H, q, *J* = 7.5, 8.3, Ar-H), 7.45-7.28 (10H, m, Ar-H), 6.71 (1H, s, CH). IR spectrum (KBr, ν_{max}, cm^{-1}): 1747 (C=O), 1597, 1545, 1504, 1452 (C=C), 1261 (C-O). MS (ESI), *m/z* (I_{rel}, %) 341.5 $[M + H]^+$ (8), 363.6 $[M + Na]^+$ (100). Found, %: C 77.37; H 4.72; N 8.26. $C_{22}H_{16}N_2O_2$. Calculated, %: C 77.63; H 4.74; N 8.23.

1-Phenyl-5-(*p*-tolyl)-3-benzoyloxy-1*H*-pyrazole (2b): Buff crystal, m.p. 89-90 °C, yield 0.71 g (85 %). ^{1}H NMR spectrum (500 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 8.16 (2H, q, *J* = 1.3, 8.3, Ar-H), 7.79 (1H, t, *J* = 7.6, Ar-H), 7.64 (2H, q, *J* = 7.6, 8.3, Ar-H), 7.45-7.16 (9H, m, Ar-H), 6.64 (1H, s, CH), 2.31 (3H, s, CH_3). IR spectrum (KBr, ν_{max}, cm^{-1}): 1745 (C=O), 1598, 1550, 1508, 1450 (C=C), 1260 (C-O). MS (ESI), *m/z* (I_{rel}, %) 355.5 $[M + H]^+$ (100), 377.5 $[M + Na]^+$ (59). Found, %: C 77.72; H 5.10; N 7.93. $C_{23}H_{18}N_2O_2$. Calculated, %: C 77.95; H 5.12; N 7.90.

5-(4-Methoxyphenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (2c): Yellow crystal, m.p. 115-116 °C, yield 0.74 g (85 %). ^{1}H NMR spectrum (500 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.16 (2H, d, *J* = 8.4, Ar-H), 7.79 (1H, t, *J* = 7.6, Ar-H), 7.64 (2H, q, *J* = 7.6, 8.4, Ar-H), 7.45-7.29 (5H, m, Ar-H), 7.21 (2H, d, *J* = 8.5, Ar-H), 6.94 (2H, d, *J* = 8.6, Ar-H), 6.61 (1H, s, CH), 3.76 (3H, s, OCH_3). IR spectrum (KBr, ν_{max}, cm^{-1}): 1744 (C=O), 1599, 1551, 1508, 1450 (C=C), 1250 (C-O). MS (ESI), *m/z* (I_{rel}, %) 371.6 $[M + H]^+$ (100), 393.5 $[M + Na]^+$ (72). Found, %: C 74.82; H 4.92; N 7.53. $C_{23}H_{18}N_2O_3$. Calculated, %: C 74.58; H 4.90; N 7.56.

5-(3,4-Dimethoxyphenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (2d): White crystal, m.p. 133-134 °C, yield 0.70 g (87 %). ^{1}H NMR spectrum (300 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.16 (2H, d, *J* = 7.2, Ar-H), 7.79 (1H, t, *J* = 7.3, Ar-H), 7.65 (2H, t, *J* = 7.3, Ar-H), 7.48-7.31 (5H, m, Ar-H), 7.00-6.80 (3H, m, Ar-H), 6.67 (1H, s, CH), 3.76 (3H, s, OCH_3), 3.57 (3H, s, OCH_3). IR spectrum (KBr, ν_{max}, cm^{-1}): 1745 (C=O), 1598, 1549, 1513, 1449 (C=C), 1257 (C-O). MS (ESI), *m/z* (I_{rel}, %) 401.5 $[M + H]^+$ (100), 423.5 $[M + Na]^+$ (27). Found, %: C 71.75; H 5.01; N 7.03. $C_{24}H_{20}N_2O_4$. Calculated, %: C 71.99; H 5.03; N 7.00.

1-Phenyl-5-(3,4,5-trimethoxyphenyl)-3-benzoyloxy-1*H*-pyrazole (2e): Yellow crystal, m.p. 128-129 °C, yield 0.75 g (87 %). ^{1}H NMR spectrum (500 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.17 (2H, d, *J* = 7.2, Ar-H), 7.79 (1H, t, *J* = 7.3, Ar-H), 7.65 (2H, t, *J* = 7.3, Ar-H), 7.49-7.35 (5H, m, Ar-H), 6.76 (1H, s, CH), 6.54 (2H, s, Ar-H), 3.67 (3H, s, OCH_3), 3.60 (6H, s, OCH_3). IR spectrum (KBr, ν_{max}, cm^{-1}): 1746 (C=O), 1586, 1545, 1506, 1445 (C=C), 1247 (C-O). MS (ESI), *m/z* (Irel, %) 431.5 $[M + H]^+$ (86), 453.5 $[M + Na]^+$ (100). Found, %: C 69.95; H 5.13; N 6.54. $C_{25}H_{22}N_2O_5$. Calculated, %: C 69.76; H 5.15; N 6.51.

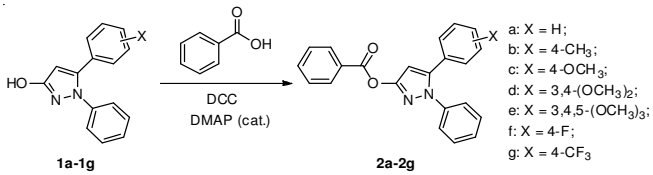
5-(4-Fluorophenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (2f): Yellow crystal, m.p. 120-121 °C, yield 0.59 g (83 %). ^{1}H NMR spectrum (500 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.16 (2H, q, *J* = 1.3, 8.3, Ar-H), 7.79 (1H, t, *J* = 7.3, Ar-H), 7.65 (2H, q, *J* = 7.3, 8.3, Ar-H), 7.45-7.22 (9H, m, Ar-H), 6.70 (1H, s, CH). IR spectrum (KBr, ν_{max}, cm^{-1}): 1745 (C=O), 1598, 1551, 1506, 1450 (C=C), 1260 (C-O). MS (ESI), *m/z* (I_{rel}, %) 359.5 $[M + H]^+$ (100), 381.5 $[M + Na]^+$ (33). Found, %: C 73.52; H 4.23; N 7.85. $C_{22}H_{15}N_2O_2F$. Calculated, %: C 73.73; H 4.22; N 7.82.

1-Phenyl-5-(4-(trifluoromethyl)phenyl)-3-benzoyloxy-1*H*-pyrazole (2g): Yellow crystal, m.p. 93-94 °C, yield 0.69 g (84 %). ^{1}H NMR spectrum (300 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.16 (2H, d, *J* = 8.4, Ar-H), 7.82-7.75 (3H, m, Ar-H), 7.65 (2H, t, *J* = 7.9, Ar-H), 7.51 (2H, d, *J* = 8.2, Ar-H), 7.47-7.32 (5H, m, Ar-H), 6.85 (1H, s, CH). IR spectrum (KBr, ν_{max}, cm^{-1}): 1747 (C=O), 1597, 1550, 1511, 1450 (C=C), 1259 (C-O). MS (ESI), *m/z* (Irel, %): 409.6 $[M + H]^+$ (100), 431.4 $[M + Na]^+$ (45). Found, %: C 67.43; H 3.69; N 6.89. $C_{23}H_{15}N_2O_2F_3$. Calculated, %: C 67.65; H 3.70; N 6.86.

RESULTS AND DISCUSSION

Two common methods are known for the formation of ester bonds. One involves the following two steps: acyl chlorides were first prepared by the acylation reaction of acids with thionyl chloride, which further proceeded dehydrochlorination with alcohols[14,15]. The other involves the condensation of acids with alcohols, using DCC as dehydrating agent and DMAP as catalyst[16,17]. In contrast to thionyl chloride, DCC is a convenient and environment-friendly reagent for the synthesis of heterocyclic ester compounds. So in our procedure, the seven novel 1,5-diaryl-3-benzoyloxy-1*H*-pyrazoles (**2a-2g**) were prepared by the DCC condensation of 1,5-diaryl-1*H*-pyrazol-3-ols

(**1a-1g**) with benzoic acid in CH_2Cl_2 as solvent. The most satisfactory results were obtained when the reactions were first stirred at 0 °C for 3 h and then at room temperature for 12 h. The crude solids were purified *via* flash chromatography to furnish good yield of **2a-2g** (**Scheme-I**).



1a-1g **2a-2g**

Scheme-I: Synthesis of 1,5-diaryl-3-benzoyloxy-1*H*-pyrazoles **2a-2g**

In the ^{1}H NMR spectra of **2a-2g**, as a result of deshielding effect of benzoyloxy group, the CH of the pyrazole ring appears as a singlet at the low field of 6.85-6.61 ppm. The aromatic protons resonated in the range of 8.17-7.64 ppm pointed out **2a-2g** have the benzoyloxy group. All products showed a multiplet of phenyl protons in the region of 7.49-6.54 ppm. The IR spectra of **2a-2g** exhibited signals at about 1745 cm^{-1} which was attributed to the characteristic absorption of C=O. Four bands at about 1600, 1550, 1510 and 1450 cm^{-1} showed the absorption feature of Ar-H. The strong bands at about 1260 cm^{-1} were the characteristic absorption of C-O.

To further validate the structures, the X-ray crystallographic analysis of 5-(3,4- dimethoxyphenyl)-1-phenyl-3-benzoyloxy-1*H*-pyrazole (**2d**) was also investigated. The detailed crystal and structure refinement data for **2d** are collected in Table-1. An ORTEP view of the **2d** molecule is shown in Fig. 1. The C-linked benzene ring A (C3-C8), N-linked benzene ring B (C12-C17) and benzoyloxy ring C (C19-C24) are twisted 50.95º, 40.62º and 64.18º, respectively, from the plane of the bridge pyrazole ring (N1/N2/C9-C11). Rings A, B and C are planar and the dihedral angles between them are 61.33º, 32.20º and 47.99º, respectively. The intermolecular hydrogen bond C-H···O links the molecules to form a three dimensional network, in which it may be effective in the stabilization of the structure (Fig. 2).

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR **2d**

Empirical formula	$C_{24}H_{20}N_2O_4$
CCDC No.	906894
Formula weight	400.42
Temperature	293(2)
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1 (No. 2)
Unit cell dimensions	a = 9.3040(19) Å α = 68.70(3)º b = 10.507(2) Å β = 81.40(3)º c = 12.075(2) Å γ = 67.99(3)º
Volume	1019.5(4) $Å^3$
Z, Calculated density	2, 1.304 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	420
Crystal size	0.10 × 0.20 × 0.30 mm
Theta range for data collection	1.81 to 25.36 deg.
Limiting indices	0 <= h <= 11, -11 <= k <= 12, -14 <= l <= 14
Reflections collected / unique	4002 / 3750 [R_{int} = 0.045]
Max. and min. transmission	0.9911 and 0.9736
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3750 / 0 / 271
Final R indices [I>2σ(I)]	R_1 = 0.0688, wR_2 = 0.1508
Largest diff. peak and hole	0.149 and -0.169 e·$Å^{-3}$

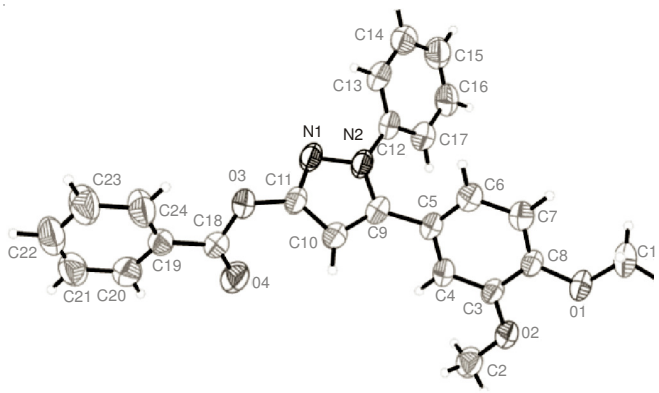


Fig. 1. Molecular structure of **2d**

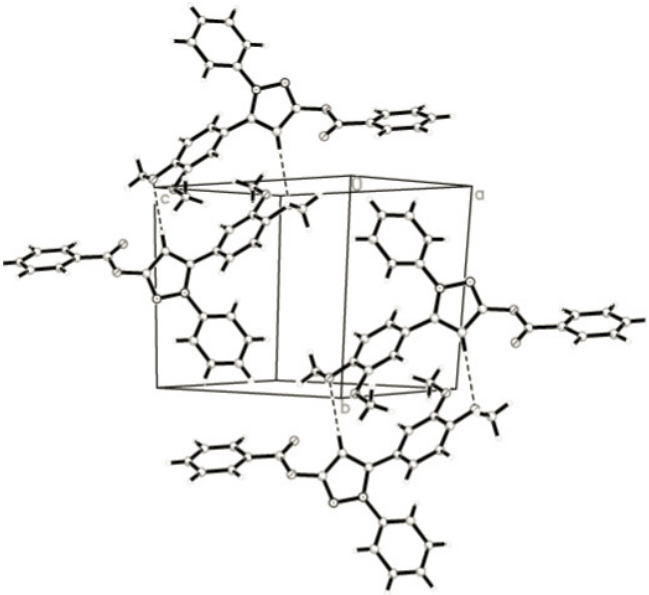


Fig. 2. A partial packing diagram of **2d** (hydrogen bonds shown by dashed lines)

Compounds **2a-2g** were screened for bioactivity against three fungi, namely *Sclerotinia sclerotiorum*, *Gibberella zeae* and *Rhizoctonia cerealis*, at a dosage of 10 mg/mL. As a result, in Table-2, most compounds have weak fungicidal activity except **2f** (X = 4-F) and **2a** (X = H) exhibiting excellent-to-medium inhibitory activity against *Sclerotinia sclerotiorum*. This might imply that the introduction of the mono-fluoro group was important for improving its fungicidal activity. In terms of substituents X, compounds with electron-withdrawing groups showed higher fungicidal activity against *Sclerotinia sclerotiorum* than that with electron-donating groups, as seen in the comparison of **2f** (X = 4-F) *vs* **2b** (X = 4-CH_3), **2c** (X = 4-OCH_3), **2d** (X = 3,4-$(OCH_3)_2$) and **2e** (X = 3,4,5-$(OCH_3)_3$). However, **2g** (X = 4-CF_3) with no inhibitory activity against *Sclerotinia sclerotiorum* was one exception, which indicated switching X from F to the strong electron-withdrawing CF_3 group had negative impact on the inhibition rates and taking the electronic effect into full consideration was significant.

Moreover, **2a** (X = H), **2b** (X = 4-CH_3) and **2c** (X = 4-OCH_3) with weak fungicidal activity against *Gibberella zeae* pointed out the introduction of the mono-substituted electron-donating groups had effective influence on their fungicidal activity. However, these compounds showed no fungicidal activity against *Rhizoctonia cerealis*. The present work indicated that **2f** and **2a** could be used as potential lead compounds for further study of novel fungicides.

TABLE-2
ANTIFUNGAL ACTIVITY OF NEWLY SYNTHESIZED COMPOUNDS (% INHIBITION)

Compounds	X	10 µg/mL		
		S. sclerotiorum	*G. zeae*	*R. cerealis*
2a	H	60	22	6
2b	4-CH_3	0	28	2
2c	4-OCH_3	18	37	1
2d	3,4-$(OCH_3)_2$	0	4	11
2e	3,4,5-$(OCH_3)_3$	0	14	5
2f	4-F	87	8	1
2g	4-CF_3	0	17	1

Conclusion

Seven novel benzoyl substituted 1,5-diaryl-3-oxypyrazoles (**2a-2g**) were synthesized by the DCC condensation. The spectroscopic and crystal data provide the useful structural information. Excellent-to-medium fungicidal activity against *Sclerotinia sclerotiorum* shown by compounds **2f** and **2a** implies that the introduction of electron-withdrawing groups to the phenyl ring by taking the electronic effect into full consideration seems to have somewhat positive effect on fungicidal activity. The most promising compounds in this study, **2f** and **2a**, can be used as potential lead compounds for further study of novel fungicides.

ACKNOWLEDGEMENTS

This work was jointly supported by the Natural Science Foundation for Young Scholars of Jiangsu Province (BK20130749) and the Youth Foundation of Southeast University ChengXian College (7303600001).

REFERENCES

1. R. Stierl, M. Scherer, W. Schrof and E.J. Butterfield, *BCPC Conf.-Pests Dis*., **1**, 261 (2000).
2. E. Ammermann, G. Lorenz, K. Schelberger, B. Mueller, R. Kirstgen and H. Sauter, *BCPC Conf - Pests Dis*., **2**, 541 (2000).
3. R. Stierl, M. Merk, W. Schrof and E.J. Butterfield, *BCPC Conf - Pests Dis*., **3**, 859 (2000).
4. Y.H. Li, R. Liu, Z.W. Yan, X.N. Zhang and H.J. Zhu, *Bull. Korean Chem. Soc*., **31**, 3341 (2010).
5. H.J. Zhu, H. Shi, H.S. Jia, Y.F. Li, G.L. Song, H.H. Liu, Y.F. Sun and J.T. Wang, CN Patent 101284815 (2008).
6. T. Konno, K. Kuriyama, H. Hamaguchi and O. Kajihara, *Brighton Crop Prot. Conf. Pests Dis*., **1**, 71 (1990).
7. Y. Miura, T. Mabuchi, M. Kajioka and I. Yanai, European Patent 361114 (1990).
8. Y.Y. Liu, H. Shi, Y.F. Li and H.J. Zhu, *J. Heterocycl. Chem*., **47**, 897 (2010).
9. Y.Y. Liu, G.K. He, K. Chen, Y.F. Li and H.J. Zhu, *J. Heterocycl. Chem*., **49**, 897 (2012).
10. Y.Y. Liu, H. Shi, G.K. He, G.L. Song and H.J. Zhu, *HeIv. Chim. Acta*, **95**, 1645 (2012).
11. A. Kocabalkanli, O. Ates and G. Otuk, *Farmaco*, **56**, 975 (2001).
12. K.M. Rajkotia and P.H. Parsania, *J. Indian Chem. Soc*., **75**, 524 (1998).
13. G.M. Sheldrick, *Acta Crystallogr. A*, **64**, 112 (2008).
14. C. Picard, N. Arnaud and P. Tisnes, *Synthesis*, 1471 (2001).
15. Y. Nagao, W.M. Dai, M. Ochiai, S. Tsukagoshi and E. Fujita, *J. Org. Chem*., **55**, 1148 (1990).
16. M.C. Duriez, T. Pigot, C. Picard, L. Cazaux and P. Tisnes, *Tetrahedron*, **48**, 4347 (1992).
17. L. Cazaux, M.C. Duriez, C. Picard and P. Tisnes, *Tetrahedron Lett*., **30**, 1369 (1989).