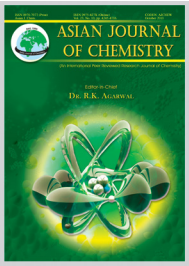
Asian Journal of Chemistry; Vol. 24, No. 5 (2012), 2249-2252

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis and Antifungal Activity of 2-Thiazoleacrylonitrile Derivatives

JIAN-QUAN WENG[1,*], ZHI-QIN YU[1], XING-HAI LIU[1] and GUO-TONG TONG[2]

[1]College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, Zhejiang, P.R. China
[2]Department of Chemical Engineering, Hangzhou Vocational and Technical College, Hangzhou 310018, Zhejiang, P.R.China

*Corresponding author: Tel: +571 88320147; E-mail: jqweng@zjut.edu.cn

(*Received*: 28 May 2011; *Accepted*: 20 December 2011) AJC-10873

A coupling reaction of 2-[4-(2,6-difluorophenyl)thiazol-2-yl]acetonitrile and desired acid chlorides were occurred in the presence of triethylamine leading to 3-hydroxy-2-thiazolylacrylonitrile derivatives, then further reacted with acid chlorides to obtain twelve novel 3-esterified-2-thiazolylacrylonitrile derivatives (yields 70.8-87.3 %). The structures of the 2-thiazoleacrylonitrile derivatives were characterized by ^{1}H NMR, mass spectra and elemental analysis. Antifungal activities against *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Colletotrichum gossypii* were also evaluated by the mycelium growth rate method. The results indicated that these compounds possess certain antifungal activity.

Key Words: Synthesis, 2-Thiazolylacrylonitrile derivative, Antifungal activity.

INTRODUCTION

Thiazole derivatives played a leading role in the field of novel agrochemicals because of their wide biological activity, such as insecticidal[1], fungicidal[2], antiviral[3], herbicidal[4] and plant-growth-regulating[5] activities. Meanwhile, acrylonitrile derivatives have gained much importance due to their diverse biological properties since 1960s[6-8]. Until 1990s, thiazolylacrylonitriles, which containing both thiazole and acrylonitrile moiety, had attracted attention and it is reported that thiazolylacrylonitriles possess the advantages of good activities and few negative influences on non-targeted organisms such as mammals, fishes and useful insects[9-11].

In view of these facts and with the aim of obtaining novel thiazolylacrylonitriles with a wide spectrum of agrochemical applications, we herein report the synthesis of a series of 2-thiazoleacrylonitrile derivatives together with their biological acivities[12-14]. In continuation to this program, some novel 2-thiazoleacrylonitrile derivatives were synthesized and their fungicidal activities were evaluated.

EXPERIMENTAL

Melting points were determined using an X-4 melting-point apparatus without calibration. The ^{1}H NMR spectra were recorded on Bruker ADVANCE III instrument (500 MHz) using TMS as an internal standard and $CDCl_3$ as solvents. Mass spectra (ESI, 70 eV) were recorded on a Therm LCQ TM Deca XP plus instrument. Elemental analyses were performed on a Vario EL elemental analyzer. The reaction progress was monitored by TLC plates run in PE-EtOAc solvent systems and spots were visualized by exposure to UV light (254 nm).

2-Bromo-1-(2,6-difluorophenyl)ethanone (**1**) was synthesized according to the literature[14], 2-cyanothioacetamide and 2-(4-(2,6-difluorophenyl)thiazol-2-yl)acetonitrile (**2**) were synthesized according to procedure reported in the reference[15]. The desired acid chlorides were commercially available.

General procedure for the synthesis of 3a and 3b: 2-[4-(2,6-Difluorophenyl)thiazol-2-yl]acetonitrile **2** (2.38 g, 10 mmol) and triethylamine (Et_3N) (1.22 g, 12 mmol) was dissolved in 40 mL of 1,4-dioxane and propionyl chloride (1.03 g, 11 mmol) or chloroacetyl chloride (1.26 g, 11 mmol) was added dropwise to the mixture. The reaction mixture was heated under reflux for 12 h, then poured into an ice/water mixture. The precipitate formed was filtered and recrystallized from ethanol to give 3-hydroxy-2-thiazolylacrylonitrile derivatives **3a** and **3b**.

Compound 3a (R_1=C_2H_5): Yellow solid, 72.2 %. m.p. 172-174 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, J = 7.5 Hz, 3H, CH_3), 2.71-2.75 (m, 2H, CH_2), 7.06-7.42 (m, 4H, ArH & thiazole-H), 15.01 (s, 1H, OH); MS (ESI) m/z ($[M+H]^+$): 293.0; Elemental anal. (%), calcd. for $C_{14}H_{10}F_2N_2OS$: C, 57.53; H, 3.45; N, 9.58; found: C, 57.47; H, 3.39; N, 9.66.

Compound 3b (R_1= CH_2Cl): Yellow solid, 70.5 %. m.p. 192-194ºC; ^{1}H NMR ($CDCl_3$) δ: 4.43 (s, 2H, CH_2Cl), 7.10-7.49 (m, 4H, ArH & thiazole-H), 15.12 (s, 1H, OH); MS (ESI) m/z ($[M+H]^+$): 313.0; Elemental anal. (%), calcd. for

$C_{13}H_7N_2OSClF_2$: C, 49.93; H, 2.26; N, 8.96; found: C, 50.07; H, 2.25; N, 9.06.

General procedure for the synthesis of 4a-l: Compound **3** (10 mmol) and triethylamine (1.22 g, 12 mmol) were dissolved in dichloromethane (20 mL) with stirring. Acid chloride (11 mmol) was added dropwise to the mixture in an ice bath. The reaction was stirred for a further 2-4 h with TLC monitoring. When the reaction was complete, the mixture was washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4 and then evaporated *in vacuo*. The residue was recrystallization from ethanol to give 3-esterified-2-thiazolylacrylonitrile derivatives (**4a-l**).

Compound 4a ($R_1 = C_2H_5$, $R_2 = CH_3$): Yellow solid, 87.3 %. m.p. 136-137 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, *J* = 7.5 Hz, 3H, CH_3), 2.58-2.62 (m, 2H, CH_2), 2.79 (s, 3H, $COCH_3$), 7.00-7.42 (m, 3H, ArH), 7.60 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 335.0; Elemental anal. (%), calcd. for $C_{16}H_{12}N_2O_2SF_2$: C, 57.48; H, 3.62; N, 8.38; found: C, 57.63; H, 3.51; N, 8.49.

Compound 4b ($R_1 = C_2H_5$, $R_2 = C_2H_5$): Yellow solid, 87.0 %. m.p. 143-145 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 1.35 (t, *J* = 7.5 Hz, 3H, $COCH_2CH_3$), 2.62-2.64 (m, 2H, CH_2), 2.72-2.74 (m, 2H, $COCH_2$), 6.99-7.42 (m, 3H, ArH), 7.62 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 349.0; Elemental anal. (%), calcd. for $C_{17}H_{14}N_2O_2SF_2$: C, 58.61; H, 4.05; N, 8.04; found: C, 58.77; H, 4.01; N, 8.11.

Compound 4c ($R_1 = C_2H_5$, $R_2 = CH_2Cl$): Yellow solid, 85.1 %. m.p. 198-200 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, *J* = 7.5 Hz, 3H, CH_3), 2.60-2.64 (m, 2H, CH_2), 5.95 (s, 3H, CH_2Cl), 7.02-7.43 (m, 3H, ArH), 7.62 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 369.0; Elemental anal. (%), calcd. for $C_{16}H_{11}N_2O_2SClF_2$: C, 52.11; H, 3.01; N, 7.60; found: C, 52.23; H, 2.97; N, 7.73.

Compound 4d (R_1=C_2H_5, R_2=$(CH_3)3C$): Yellow solid, 74.1 %. m.p. 201-204 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, *J* = 7.5 Hz, 3H, CH_3), 2.90-2.94 (m, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$), 6.98-7.37 (m, 3H, ArH), 7.60 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 377.0; Elemental anal. (%), calcd. for $C_{19}H_{18}N_2O_2SF_2$: C, 60.62; H, 4.82; N, 7.44; found: C, 60.77; H, 4.75; N, 7.58.

Compound 4e ($R_1 = C_2H_5$, $R_2 = C_6H_5$): Yellow solid, 79.1 %. m.p. 157-159 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 2.71-2.74 (m, 2H, CH_2), 6.94-8.22 (m, 8H, ArH), 7.61 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 397.0; Elemental anal. (%), calcd. for $C_{21}H_{14}N_2O_2SF_2$: C, 63.63; H, 3.56; N, 7.07; found: C, 63.75; H, 3.49; N, 7.16.

Compound 4f ($R_1 = C_2H_5$, $R_2 = 4\text{-}ClC_6H_4$): Yellow solid, 81.2 %. m.p. 151-153 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 2.73-2.75 (m, 2H, CH_2), 7.25-8.28 (m, 7H, ArH), 7.63 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 431.0; Elemental anal. (%), calcd. for $C_{21}H_{13}N_2O_2SClF_2$: C, 58.54; H, 3.04; N, 6.50; found: C, 58.70; H, 3.00; N, 6.59.

Compound 4g ($R_1 = CH_2Cl$, $R_2 = CH_3$): Yellow solid, 85.7 %. m.p. 154-156 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.43 (s, 2H, CH_2Cl), 2.80 (s, 3H, CH_3), 7.02-7.42 (m, 3H, ArH), 7.64 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 355.0; Elemental anal. (%), calcd. for $C_{15}H_9N_2O_2SClF_2$: C, 50.78; H, 2.56; N, 7.90; found: C, 50.83; H, 2.52; N, 7.97.

Compound 4h ($R_1 = CH_2Cl$, $R_2 = C_2H_5$): Yellow solid, 84.4 %. m.p. 163-165 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.41 (s, 2H, CH_2Cl), 1.37 (t, *J* = 7.5 Hz, 3H, CH_3), 2.75-2.77 (m, 2H, $COCH_2$), 7.02-7.45 (m, 3H, ArH), 7.63 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 369.0; Elemental anal. (%), calcd. for $C_{16}H_{11}N_2O_2SClF_2$: C, 52.11; H, 3.01; N, 7.60; found: C, 52.24; H, 2.97; N, 7.68.

Compound 4i ($R_1 = CH_2Cl$, $R_2 = CH_2Cl$): Yellow solid, 83.1 %. m.p. 205-206 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.44 (s, 2H, CH_2Cl), 5.97 (s, 3H, $COCH_2Cl$), 7.03-7.45 (m, 3H, ArH), 7.65 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 389.0; Elemental anal. (%), calcd. for $C_{15}H_8N_2O_2SCl_2F_2$: C, 46.29; H, 2.07; N, 7.20; found: C, 46.40; H, 2.04; N, 7.31.

Compound 4j ($R_1 = CH_2Cl$, $R_2 = (CH_3)_3C$): Yellow solid, 70.8 %. m.p. 209-211 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.39 (s, 2H, CH_2Cl), 1.39 (s, 9H, $C(CH_3)_3$), 7.01-7.42 (m, 3H, ArH), 7.62 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 397.0; Elemental anal. (%), calcd. for $C_{18}H_{15}N_2O_2SClF_2$: C, 54.48; H, 3.81; N, 7.06; found: C, 54.62; H, 3.76; N, 7.14.

Compound 4k ($R_1 = CH_2Cl$, $R_2 = C_6H_5$): Yellow solid, 76.5 %. m.p. 172-174 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.44 (s, 2H, CH_2Cl), 6.99-8.24 (m, 8H, ArH), 7.63 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 417.0; Elemental anal. (%), calcd. for $C_{20}H_{11}N_2O_2SClF_2$: C, 57.63; H, 2.66; N, 6.72; found: C, 57.75; H, 2.61; N, 6.76.

Compound 4l ($R_1 = CH_2Cl$, $R_2 = 4\text{-}ClC_6H_4$): Yellow solid, 79.0 %. m.p. 169-170 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.45 (s, 2H, CH_2Cl), 7.27-8.28 (m, 7H, ArH), 7.64 (s, 1H, thiazole-H); MS (ESI) m/z ($[M+H]^+$): 451.0; Elemental anal. (%), calcd. for $C_{20}H_{10}N_2O_2SCl_2F_2$: C, 53.23; H, 2.23; N, 6.21; found: C, 53.37; H, 2.20; N, 6.28.

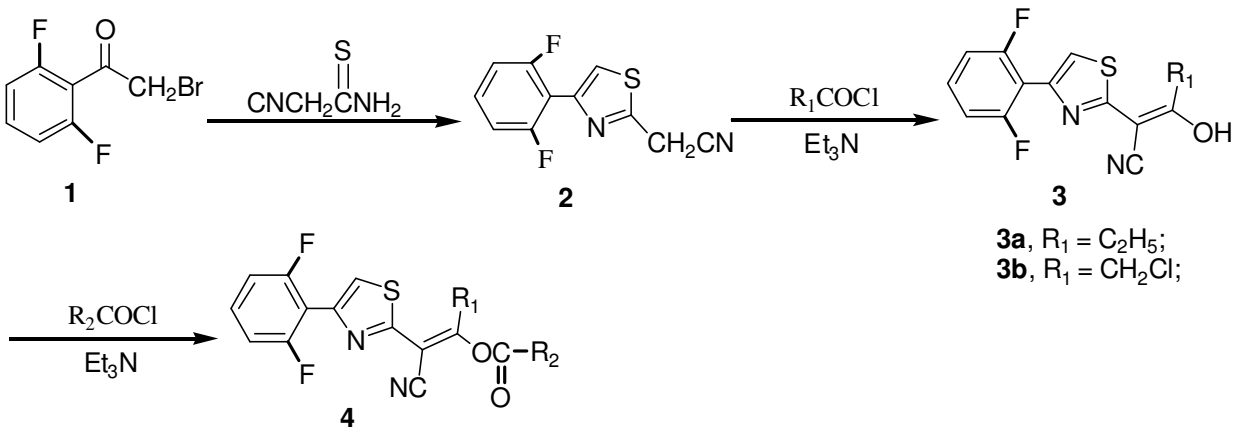
Antifungal activity assays: Antifungal activities of compounds **3** and **4** against *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Colletotrichum gossypii* were evaluated using mycelium growth rate test according work of Mu[16]. Culture media, with 100 mg/L concentration of the test compounds, were obtained by mixing the solution of compounds **3** and **4** with potato dextrose agar (PDA), on which fungus cakes were placed. The cultures were carried out at 24 ± 1 ºC for 96 h. Propiconazole, a commercial fungicide, was used as a control and sterile water was used as a blank. Three replications were performed in antifungal activity assays. The relative inhibition rate of the circle mycelium compared to blank assay was calculated *via* the following equation:

$$\text{Relative ratio } \% = (N_S - N_C)/N_C \times 100\ \%$$

where, N_S is the extended diameter of the circle mycelium during the blank assay and N_C is the extended diameter of the circle mycelium during testing.

RESULTS AND DISCUSSION

The synthetic route to the title compounds **4a-l** is shown in **Scheme-I**. 3-Hydroxy-2-thiazolylacrylonitrile derivatives **3a** and **3b** were synthesized from a coupling reaction of 2-[4-(2,6-difluorophenyl)thiazol-2-yl]acetonitrile (**2**) and desired acid chlorides at refluxing temperature in the presence of triethylamine. The structure of **3** were the enol-form rather than the ketone-form, due to the influence of the large conjugated



4a, $R_1 = C_2H_5$, $R_2 = CH_3$; **4b**, $R_1 = C_2H_5$, $R_2 = C_2H_5$; **4c**, $R_1 = C_2H_5$, $R_2 = CH_2Cl$;
4d, $R_1 = C_2H_5$, $R_2 = (CH_3)_3C$; **4e**, $R_1 = C_2H_5$, $R_2 = C_6H_5$; **4f**, $R_1 = C_2H_5$, $R_2 = 4\text{-}ClC_6H_4$;
4g, $R_1 = CH_2Cl$, $R_2 = CH_3$; **4h**, $R_1 = CH_2Cl$, $R_2 = C_2H_5$; **4i**, $R_1 = CH_2Cl$, $R_2 = CH_2Cl$;
4j, $R_1 = CH_2Cl$, $R_2 = (CH_3)_3C$; **4k**, $R_1 = CH_2Cl$, $R_2 = C_6H_5$; **4l**, $R_1 = CH_2Cl$, $R_2 = 4\text{-}ClC_6H_4$;

Scheme-I Synthetic route for compounds **4a-l**

TABLE-1
ANTIFUNGAL ACTIVITIES OF COMPOUNDS **3** AND **4** *IN VITRO* AT 100 mg/L

No.	*Fusarium oxysporium*	*Rhizoctonia solani*	*Botrytis cinereapers*	*Gibberella zeae*	*Colletotrichum gossypii*
3a	50.2	65.0	58.1	67.9	77.3
3b	70.0	56.3	87.1	46.4	59.1
4a	20.0	36.3	34.5	36.4	29.6
4b	20.0	34.0	39.1	44.8	37.2
4c	30.8	41.3	43.5	41.0	26.1
4d	21.0	29.0	30.6	28.5	31.8
4e	16.3	21.1	29.2	24.0	19.0
4f	48.5	43.6	33.3	40.3	47.1
4g	31.4	27.1	46.8	26.0	21.0
4h	28.0	24.5	50.2	31.2	24.6
4i	42.2	32.8	56.5	28.5	13.5
4j	34.0	18.0	47.9	17.5	20.0
4k	26.5	20.2	38.0	19.3	12.3
4l	50.4	34.2	42.6	32.4	37.5
propiconazole	90.0	90.5	0.0	0.0	87.5

system formed by the thiazole ring, CN and C=C and in the ^{1}H NMR spectrum of **3**, the -OH proton signals were observed at *ca.* 15.00 ppm as a singlet. In previous work, it is found that comound **3** bearing a alkyl group, especially **3a** ($R_1 = C_2H_5$) and **3b** ($R_1 = CH_2Cl$), exhibited higher fungicidal activities than those bearing a aryl group[13]. In this article, we planned to further optimize the structures of compounds **3a** and **3b** for improving their antifungal activity. Thus, the reactions of **3** with a series of acid chlorides were occurred in the presence of triethylamine, leading to the desired compounds (**4a-l**) in 70.8-87.3 % yields. All the compounds were identified and characterized by ^{1}H NMR, mass spectra and elemental analysis. In the ^{1}H NMR spectrum of **4**, thiazole-H proton signals were observed at about 7.60 ppm as a singlet and the Ph-H proton signals were observed at 6.94-8.28 ppm as a multiplet. Meanwhile, all of compounds **4** exhibited $(M+H)^+$ peak in the ESI-MS results.

Antifungal activities: The antifungal activity of all the compounds **3** and **4** against *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae and Colletotrichum gossypii* has been investigated at the dosage of 100 mg/L compared with the control fungicide (propiconazole). The results of antifungal activity testing are listed in Table-1. The results of bioassay showed that all compounds exhibited certain antifungal activity against all the tested fungi, whereas the control fungicide (propiconazole) showed no activity against *Botrytis cinereapers* and *Gibberella zeae*. Some of them exhibited moderate antifungal activity, for example, compounds **3a** and **3b** possessed above 50 % inhibitory activities against *Fusarium oxysporium*, *Rhizoctonia solani* and *Colletotrichum gossypii*, but their activities were still lower than that of propiconazole. Meanwhile, compound **3b** showed 87.1 % inhibition against *Botrytis cinereapers*. It was not as good as we expected that, in general, compounds **4** displayed lower antifungal activity than compounds **3**, which indicated that the presence of hydroxyl group enhanced the activity of the compounds. From this result, this type of compound could be further developed as potential fungicides, but the hydroxyl group in compounds should be mantained.

Conclusion

In summary, a coupling reaction of 2-[4-(2,6-difluorophenyl)thiazol-2-yl]acetonitrile **2** and desired acid chlorides were occurred in presence of triethylamine leading to 3-hydroxy-2-thiazolylacrylonitrile derivatives **3a** and **3b**. And then, twelve novel 3-esterified-2-thiazolylacrylonitrile derivatives **4** were synthesized by the reactions of **3** with desired acid chlorides in presence of triethylamine. The structures of these compounds were characterized by ^{1}H NMR, mass spectra and elemental analysis. The results of preliminary bioassay indicated that these compounds possess certain antifungal activity against *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae*, *Colletotrichum gossypii* and could be further developed as potential fungicides.

ACKNOWLEDGEMENTS

This work was funded by National Natural Science Foundation of China (No. 30900959, 21002090); the Key Laboratory of Green Fine Chemistry and Application, Hangzhou, Zhejiang, PR China (No. KFJ2011005); and Undergraduate Educational Innovation Program of Zhejiang University of Technology (No. 2011).

REFERENCES

1. Z.Z. Zhou, Q. Chen and G.F. Yang, *Chin. J. Org. Chem.*, **28**, 1385 (2008).
2. A.X. Hu, L.M. He, M.Y. Dong, J.Y. Zhang and X.M. Ou, *Chem. J. Chin. Univ.*, **29** 739 (2008).
3. W. Wang, G.P. Zhang, B.A. Song, H. Wang, L.H. Jin, D.Y. Hu and S. Yang, *Chin. J. Org. Chem.*, **27**, 279 (2007).
4. Q.M. Wang, H. Li, Y.H. Li and R.Q. Huang, *J. Agric. Food Chem.*, **52**, 1918 (2004).
5. P.C. David, V.E. Roy and T.H. Roy, *J. Agric. Food Chem.*, **29**, 640 (1981).
6. S.A. Heininger and G.H. Birum, US Patent 3065127 (1962).
7. T. Koyanagi, Y. Nakamura, M. Morita, K. Sugimoto, T. Ikeda and M. Ogawa, US Patent 6187944 (2001).
8. Y. Shibata, N. Ichikawa, R. Hatano and S. Makita, JP Patent 2004010577 (2004).
9. T. Ogura, H. Murakami, R. Miyachi, T. Nagaoka, T. Miyake, N. Mimori, S. Takii and Y. Inoue, WO Patent 9633995 (1996).
10. T. Iwasa, R. Hatano, D. Hanai, T. Yagihara, Y. Shibata, T. Suzuki, S. Suga, Y. Kubota and H. Furukawa, WO Patent 2003064401 (2003).
11. H. Murakami and S. Takii, WO Patent 2007100160 (2007).
12. P. Yang, J.Q. Weng, C.X. Tan and X.L. Wang, *Chin. J. Org. Chem.*, **29**, 2000 (2009).
13. P. Yang, D.L. Shen, C.X. Tan, J.Q. Weng, Q. Lu, Y.C. Wei and X.L. Kong, *Chin. J. Pestic. Sci.*, **10**, 371 (2008).
14. J.Q. Weng, H.J. Liu, X.H. Liu, C.X. Tan and D.L. Shen, *Chin. J. Pestic. Sci.*, **12**, 463 (2010).
15. P. Yang, C.X. Tan, D.L. Shen, Q. Fu and X.L. Kong, *J. Zhejiang Univ. Tech.*, **35**, 19 (2007).
16. L.Y. Mu, Research Method of Plant Chemical Protection, China Agriculture Press, Beijing, China, 76 (1994).