A concise synthesis of azoxystrobin using a Suzuki cross-coupling reaction

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A simple, efficient and eco-friendly process for the synthesis in good yield of azoxystrobin from 2-bromophenol has been developed using phenolic hydroxyl protection, Grignard reaction, Suzuki cross-coupling, hydrogenation and a nucleophilic reaction on a 2-chloropyrimidine.

Keywords: strobilurins, Suzuki cross-coupling reaction, azoxystrobin, hydrogenation

Modern agricultural practices rely strongly on the use of the fungicidal strobilurins, which can increase crop yield to feed an ever-growing human population with high quality and inexpensive foods.[1] Strobilurins, mainly consisting of 16 compounds, occupy 15% of the total fungicide market share and represent the second most important fungicide group worldwide.[2] Azoxystrobin, developed by Syngenta is a typical representative of the strobilurin fungicide family.[3] It shows many excellent properties, such as strong biological activity, a broad antifungal spectrum, good photochemical stability, low toxicity towards mammalian cells and benign environmentally characteristics.[4] Due to the positive attributes of azoxystrobin, its global annual sales were up to $1.2 billion in 2011, and it is predicted that the global annual sales of azoxystrobin will exceed $3.5 billion with its global consumption likely to reach about 13×10^6 kg in 2015.[5]

There are numerous ways to synthesise azoxystrobin. Generally it is preferred to construct the methyl α-phenyl-β-methoxyacrylate group at an early stage and then build on the central pyrimidinyloxy and terminal cyanophenoxy rings. In a typical traditional synthetic approach to azoxystrobin, the (*E*)-methyl-2-(2-hydroxyphenyl) -3-methoxyacrylate can be reacted with 4,6-dichloropyrimidine under alkaline condition in *N,N*-dimethylformamide to form (*E*)-methyl-2-[2-(6-chloropyrimidin-4-yloxy) phenyl]-3-methoxyacrylate which is then reacted with 2-cyanophenol in an Ullmann-type coupling process.[6]

Although a plethora of reports has been established on the development of synthetic routes to azoxystrobin, there are still many problems in its industrial production. Scheme 1 shows three basic synthetic routes to azoxystrobin. As far as route **1** is concerned, the toxic substance DMS (dimethylsulfate) is necessary when synthesising the intermediate **a**, and the total yield is only 23.8%.[7] As for the route **2**, the intermediate **b** is an allergic substance, and the ring-opening reaction of compound **c** generates some non-environmentally friendly by-products, such as methyl benzofuran-3-carboxylate. Its total yield is also below 30%.[8] In terms of route **3**, sodium hydride, which is inflammable is involved, and high boiling point solvent NMP, *i.e. N*-methylpyrrolidone is also employed, which was prohibited by the European Union in 2003 as a toxic substance that affects fertility.[6]

The Suzuki cross-coupling reaction is an efficient and remarkably effective method for carbon–carbon bond formation in both the laboratory and industry, especially for the preparation of advanced materials, agrochemicals and pharmaceutical compounds.[9] The Suzuki cross-coupling reaction is superior to other coupling reactions, since it can be carried out under conventional reaction conditions with a wide range of functional group tolerance. Furthermore, it is unaffected by aqueous solvent, and it generates non-toxic by-products which can be separated easily.[10]

We report here a concise synthetic approach to azoxystrobin, starting from a raw material with relatively low cost, 2-bromophenol, and using a Suzuki cross-coupling reaction as the key step.

Result and discussion

As can be seen from Scheme 1, 2-cyanophenol, 4, 6-dichloropyrimidine and (*E*)-methyl-3-methoxy-2-(2-hydroxyphenyl) acrylate make up the main structural framework of azoxystrobin. Since 2-cyanophenol and 4, 6-dichloropyrimidine are commercial available, the generation of (*E*)-methyl-3-methoxy-2-(2-hydroxyphenyl) acrylate, compound (**5**),[7] becomes the key step in its synthesis. In our route (Scheme 2), the synthesis of the precursor of (**5**), compound (**4**), from arylboronic acid (**2**) and (*Z*)-methyl-2-iodo-3- methoxyacrylate (**3**)[11] depended on Suzuki–Miyaura cross-coupling reaction as the crucial step.[12, 13] Optimum reaction conditions should be selected in order to obtain the highest yield. Table 1 records the effects of different mole ratios of reactants on the yield of compound (**4**).

Table 1 shows that the yield of compound (**4**) is already up to 94% when the mole ratio of arylboronic acid to (Z)-methyl-2-iodo-3- methoxyacrylate is 1:1. This is due to the high stereoselectivity of the Suzuki–Miyaura cross-coupling reaction. If mole ratio and isolated yield are taken into account, entry 4 represents the optimal conditions.

Table 2 records the effects of varying catalyst amounts on the yield of compound (**4**).

As can be seen, the yield of compound (**4**) reaches a maximum of 95.7% when the amount of catalyst $Pd(PPh_3)_4$ is 0.05 mol per mol of compound (**3**) (entry 3). Greater amounts of catalyst affects the efficient separation of product, and results in a lower yield (entries 5 and 6). In addition, the coordination compound formed by the catalyst is prone to perform an aryl

Table 1 Effects of mole ratio of reactants on the yields of compound (**4**)

Entry	Arylboronic acid **2**/equiv.	Isolated yield/%
1	1.0	93.9
2	1.1	94.3
3	1.2	95.0
4	1.3	95.7
5	1.4	95.8
6	1.5	95.8

Reaction conditions: iodoacrylate (**3**) (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (3.0 equiv.), in 1,4-dioxane/H_2O (3:1 v/v) (8 mL), 90 °C, 10 h.

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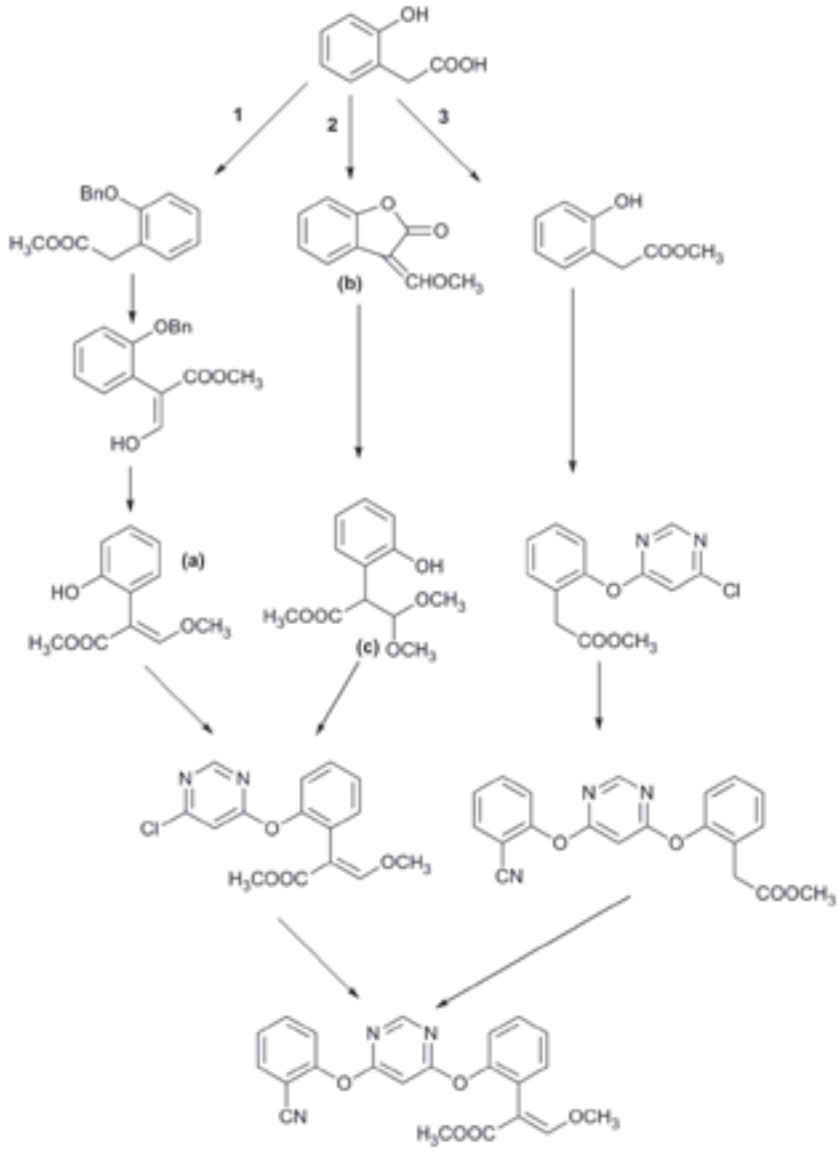
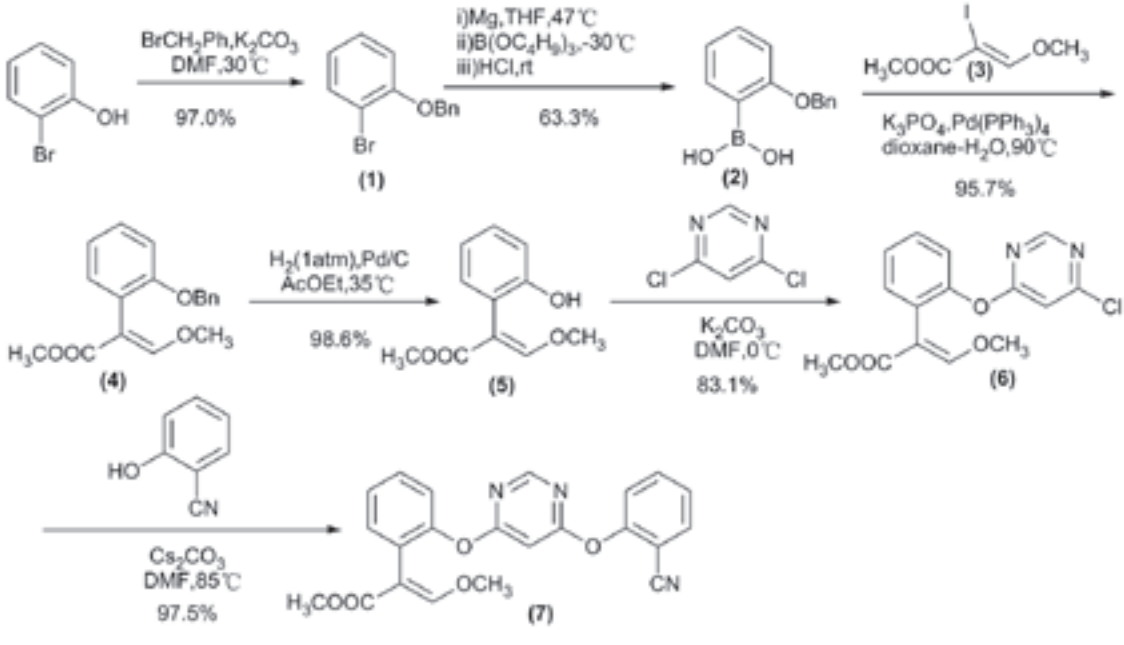


Scheme 1 Three traditional synthetic routes to azoxystrobin (**1, 2** and **3**).



Scheme 2 Concise synthesis route of azoxystrobin.

Table 2 Effects of varying the amounts of $Pd(PPh_3)_4$ on the yields of compound (**4**) (Scheme 2)

Entry	$Pd(PPh_3)_4$/equiv.	Isolated yield/%
1	1/10	84.9
2	1/15	90.6
3	1/20	95.7
4	1/25	91.0
5	1/30	85.9
6	1/35	82.7

Reaction conditions: iodoacrylate (**3**) (1.0 equiv.), arylboronic acid **2** (1.3 equiv.), K_3PO_4 (3.0 equiv.), in 1,4-dioxane/H_2O (3:1 v/v) (8 mL), 90 °C, 10 h.

Table 3 Effects of varying the solvent composition on the yields of compound (**4**) (Scheme 2)

Entry	$v_{1,4\text{-Dioxane}}$:v_{H2O}	Isolated yield/%
1	1:1	35.4
2	3:1	95.7
3	5:1	88.7
4	10:1	84.8
5	20:1	73.6
6	No water	71.5

Reaction conditions: iodoacrylate (**3**) (1.0 equiv.), arylboronic acid (**2**) (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (3.0 equiv), solvent (8 mL), 90 °C, 10 h.

exchange reaction. Lower amounts of catalyst also lowers the yield (entries 1 and 2)

Table 3 records the effects of solvent composition on the yields of compound (**4**).

As the data indicate, suitable amounts of water promote the reaction (entries 1–6). According to the reaction mechanism of the Suzuki reaction, a tetravalent borate intermediate with strong electronegativity can be formed by arylboronic acid and alkali. The intermediate can accelerate the nucleophilic reaction of organic groups on the boron atom. The presence of water favours of the formation of the tetravalent borate intermediate, and causes the higher yield.

Therefore, the optimum reaction conditions for the preparation of compound (**4**) in the key step of the synthesis of azoxystrobin is iodoacrylate (**3**) (1.0 equiv.), arylboronic acid (**2**) (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (3.0 equiv), in 1,4-dioxane/H_2O (3:1 v/v) (8 mL), at 90 °C for 10 h.

All compounds were characterised by their IR, ^{1}H NMR and LC-MS spectra.

Experimental

NMR spectra were obtained on a Bruker AM-400 spectrometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in Hz. ESI mass spectra were determined on a Varian-310 LC-MS spectrometer (Varian, China). IR spectra were obtained on a 640-IR FTIR spectroscopy (Varian, USA) using KBr powder as diluent. Melting points were determined on a RY-1 apparatus (Tianfen, China). Commercial reagents and solvents were provided by Sinopharm Chemical Reagent Co. (China). All chemicals were analytical reagent grade and were used without any pretreatment, except tetrahydrofuran which was distilled immediately before use from sodium-benzophenone ketyl.

1-(Benzyloxy)-2-dibromobenzene (**1**): Benzyl bromide (1.19 g, 6.94 mmol) was added to a solution of 2-bromophenol (1.00 g, 5.78 mmol) and anhydrous K_2CO_3 (0.88 g, 6.36 mmol) in dry DMF (11.6 mL) under a nitrogen atmosphere. The mixture was stirred at 30 °C for 3.5 h, poured into water and extracted with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel using hexane as eluent, to afford **1** as a colourless liquid (1.48 g, 97.0%); IR (KBr, ν_{max}/cm^{-1}): 3050, 750; ^{1}H NMR: δ 7.67 (d, 1H, *J* = 7.76 Hz), 7.58 (d, 2H, *J* = 7.14 Hz), 7.51–7.48 (m, 2H), 7.44–7.42 (m, 1H), 7.34–7.30 (m, 1H), 7.02 (d, 1H, *J* = 8.23 Hz), 6.96–6.92 (m, 1H), 5.22 (s, 2H); LC-MS (ESI): calcd for $C_{13}H_{11}NaO^{79}Br$([M+Na]$^+$): 285.2; found: 285.0; calcd for $C_{13}H_{11}NaO^{81}Br$([M+Na]$^+$): 287.2; found: 287.0.

[2-(Benzyloxy)phenyl]boronic acid (**2**): Magnesium shavings (0.22 g, 9.13 mmol) and one crystal of iodine were added to a flask slowly and heated to 35 °C under a nitrogen atmosphere, and then 3–5 drops of solution of compound **1** (2.00 g, 7.61 mmol) in dry THF (12 mL) were added. After keeping the reaction mixture at 47 °C for 5 min without stirring, the rest of the mixture was added dropwise into the flask with stirring, during which the iodine started to fade. Simultaneously, the flask was replenished with dry THF (4 mL). The reaction mixture was kept at 47 °C for 2 h, and then cooled to room temperature. Finally, it was added dropwise over a period of 30 min to a stirred solution of tri-*n*-butylborate (3.50 g, 15.21 mmol) in THF (7 mL) at –30 °C. 2 h later, the solution was warmed to room temperature and stirred for a further 2 h. The reaction was quenched by adding 37% HCl aqueous (4 mL). 30 min later, the solution was extracted with ether. The combined ether extracts were then extracted with 1 M NaOH (45 mL). A grey white precipitate then formed which was removed by filtration. The resulting precipitate, namely a basic salt was reacted with 37% HCl aqueous once again to obtain a white precipitate, which was then collected by vacuum filtration and washed with a little cold water and dried to afford **2** (1.10 g, 63.3%); m.p. 108–109 °C; IR (KBr, ν_{max}/cm^{-1}): 3400, 1341, 759; ^{1}H NMR: δ 7.89 (d, 1H, *J* = 7.29 Hz), 7.48–7.39 (m, 6H), 7.10–7.06 (m, 1H), 7.01 (d, 1H, *J* = 8.22 Hz), 5.74 (s, 2H), 5.17 (s, 2H); LC-MS (ESI): calcd for $C_{13}H_{11}BO_3$([M-2H]$^+$): 226.1; found: 226.2.

(Z)-Methyl-2-iodo-3-methoxyacrylate (**3**): Iodine (6.57 g, 25.86 mmol) dissolved in CCl_4/pyridine (1:1 v/v) (60 mL) was added dropwise, under an atmosphere of nitrogen to a solution of (*E*)-methyl methoxyacrylate (1.00 g, 8.62 mmol) in CCl_4/pyridine (1:1 v/v) (20 mL) at 0 °C. The mixture was stirred for 72 h during which time it was allowed to warm to room temperature. The mixture was diluted with ether (100 mL) and washed successively with H_2O (50 mL), 37% HCl (2 x 4 mL), H_2O (50 mL), $Na_2S_2O_3$ (5.00 g) and dried over anhydrous $MgSO_4$, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using (hexane/EtOAc=8:1 v/v) as eluent, to afford **3** (1.48 g, 70.9%); m.p. 51–52 °C (lit.[14] 51–51.5 °C); IR (KBr, ν_{max}/cm^{-1}): 1711, 1621, 754; ^{1}H NMR: δ 7.67 (s, 1H), 3.77 (s, 3H), 3.97 (s, 3H); LC-MS (ESI): calcd for $C_5H_7O_3I$ ([M]$^+$):242.0; found:242.1.

*(*E*)-Methyl-3-methoxy-2-(2-phenoxyphenyl)acrylate* (**4**): A mixture of iodoacrylate **3** (1.00 g, 4.13 mmol), arylboronic acid **2** (1.23 g, 5.37 mmol), K_3PO_4 (2.63 g, 12.40 mmol) and $Pd(PPh_3)_4$ (0.24 g, 0.21 mmol) in a mixture of dioxane (6 mL) and water (2 mL), previously degasified by bubbling nitrogen under ultrasonic irradiation for a period of 15 min, was stirred under nitrogen at 90 °C for 10 h. Then the reaction mixture was cooled, poured into water and extracted with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel using (hexane/EtOAc=8:1 v/v) as eluent, to afford **4** (1.18 g, 95.7%); m.p. 76–77°C (lit.[15] 76–77 °C); IR (KBr, ν_{max}/cm^{-1}): 1703, 1641; ^{1}H NMR: δ 7.53 (s, 1H), 7.43–7.32 (m, 5H), 7.31–7.29 (m, H), 7.27–7.23 (m, 1H), 7.03–6.97 (m, 2H), 5.10 (s, 2H), 3.82 (s, 3H), 3.67 (s, 3H); LC-MS (ESI): calcd for $C_{18}H_{19}O_4$([M+H]$^+$): 299.3; found: 299.2.

*(*E*)-Methyl-3-methoxy-2-(2-hydroxyphenyl) acrylate* (**5**): A mixture of 10 wt % Pd/C (0.35 g, 0.17 mmol) and compound **4** (2.00 g, 6.71 mmol) in 47 mL EtOAc was stirred under H_2 atmosphere (1 atm) at 35 °C for 12 h. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using (hexane/EtOAc=3:1 v/v) as eulent, to afford **5** (1.38 g, 98.6%); m.p. 125–126 °C (lit.[15] 125–126 °C); IR (KBr, ν_{max}/cm^{-1}): 3401, 1679; ^{1}H NMR: δ 7.66 (s, 1H), 7.25 (d, 1H, *J* = 7.86 Hz), 7.19 (d, 1H, *J* = 7.92 Hz),7.01–6.95 (m, 2H), 6.20 (s, 1H), 3.91 (s, 3H), 3.80 (s, 3H); LC-MS (ESI): calcd for $C_{11}H_{12}NaO_4$([M+Na]$^+$): 231.2; found: 231.1.

(E)-Methyl-2-(2-((6-chloropyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (**6**):[7] A mixture of compound **5** (2.00 g, 9.62 mmol), K_2CO_3 (2.65 g, 19.23 mmol) and 4,6-dichloropyrimidine (2.87 g, 19.23 mmol) was dissolved in dry DMF (69.2 mL) at 0 °C under nitrogen. The mixture was stirred at this temperature for 12 h, poured into water and extracted with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel using (hexane/EtOAc=8:1 v/v) as eluent, to afford **6** (2.56 g, 83.1%); m.p. 103–104 °C (lit.[16] 103–104 °C); IR (KBr, ν_{max}/cm^{-1}): 1708, 1631; ^{1}H NMR: δ 8.60 (s, 1H), 7.49 (s, 1H), 7.46–7.42 (m, 1H), 7.38–7.34 (m, 2H), 7.19 (d, 1H, *J* = 8.00 Hz), 6.81 (s, 1H), 3.76 (s, 3H), 3.62 (s, 3H); LC-MS (ESI): calcd for $C_{15}H_{13}ClO_4N_2$([M]$^+$): 320.7; found: 321.0.

Azoxystrobin (**7**):[5] A mixture of compound **6** (2.00 g, 6.24 mmol), Cs_2CO_3 (4.07 g, 12.48 mmol) and 2-cyanophenol (1.49 g, 12.48 mmol) in dry DMF (43 mL) was stirred at 85 °C under nitrogen for 7 h. The resulting orange suspension was cooled to room temperature, poured into water and extracted with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel using (hexane/EtOAc=4:1v/v) as eluent, to afford **7** (2.45 g, 97.5%); m.p. 115–116 °C (lit.[17] 117–118 °C); IR (KBr, ν_{max}/cm^{-1}): 2230, 1707; ^{1}H NMR: δ 8.43 (s, 1H), 7.75–7.67 (m, 2H), 7.52 (s, 1H), 7.44–7.32 (m, 5H), 7.25 (d, 1H, *J* = 7.87 Hz), 6.44 (s, 1H), 3.78 (s, 3H), 3.66 (s, 3H); LC-MS (ESI): calcd for $C_{22}H_{18}O_5N_3$([M+H]$^+$): 404.4; found: 404.1.

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References

1 D.G. Brooke and J.C. Morris, *Tetrahedron Lett*., 2008, **49**, 2414.
2 C.C. Howell, K.T. Semple and G.D. Bending, *Chemosphere*, 2014, **95**, 370.
3 F.Q. Yang, T.Y. Zhang, Q.H. Liu, G.Q. Xu, Y.B. Zhang, S. Zhang and Y. Ito, *J. Chromatogr. A*., 2000, **883**, 67.
4 X. Zhang, H.J. Liu, Y.X. Gao, H.L. Wang, B.Y. Guo and J.Z. Li, *Chin. J. Chem*., 2012, **30**, 1517.
5 P. Javier, M. Josep V, A. Consuelo, A.S. Antonio and A.F. Antonio, *Toxicol. Lett*., 2012, **210**, 240.
6 A.J. David, P.M. James and R.S. Mark, Patent, US7084272, 2006.
7 K. Mika, T. Kazuyuki, H. Hiroshi, Y.M. Yukie, U. Mikiko, S. Machiko, W. Eiki, L. Seiji, N. Hiroshi and M. Shiro, *J. Agr. Food Chem*., 2012, **60**, 904.
8 X. Zhang, Y.X. Gao, H.J. Liu, B.Y. Guo and H.L. Wang, *Bull. Korean Chem. Soc*., 2012, **33**, 2627.
9 P. Dilip K, D. Sandip, C. Kamal R, K. Mayur V, B. Bhalachandra M and J. Vimal K, *Tetrahedron Lett., 2014, **55**,* 2953.
10 I.H. Mansoor, R. Nasir, A. Gulraiz, C.G. Abbas, M.S. Ghulam, Z. Muhammad, R.U. Ali, Z.U.H. Muhammad and J.H. Ze, *Molecules*, 2015, **20**, 5202.
11 C.R. Johnson, J.P. Adams, M.P. Braun, C.B.W. Senanayake, P.M. Wovkulich and M.R. Uskokovlc, *Tetrahedron Lett., 1992, **33**, 917.*
12 N. Miyaura and A. Suzuki, *Chem. Rev*., 1995, **95**, 2457.
13 A.A. Peshkov, V.A. Peshkov and O.P. Pereshivko, *J. Org. Chem*., 2015, **80**, 6598.
14 R.S. Coleman and X.L. Lu, *Chem. Commun*., 2006, **4**, 423.
15 J.M. Clough and C.R.A. Godfrey, Patent, EP260794, 1988.
16 P. Yang, Y.K. Liu and Z.Y. Xu, *World Pesticides*, 2013, **35**, 26.
17 H.B. Christensen and K. Granby, *Food Addit. Contam. A*., 2011, **18**, 866.