Full Paper

# A New Manufacturing Route to Picoxystrobin

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# A New Manufacturing Route to Picoxystrobin

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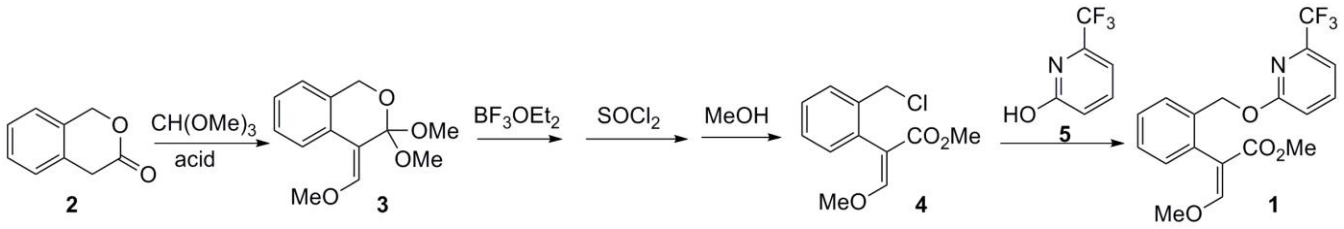
TOC graphic


CH(OMe)3
acid
BF3OEt2
SOCl2
MeOH
CF3
N
HO
5
Cl
CO2Me
MeO
OMe
2
3
4
1

ABSTRACT: A new and efficient manufacturing technology is disclosed in present work for the preparation of picoxystrobin, in which all the intermediates can be used directly for the next step without purification.

Key Words: picoxystrobin, strobilurin fungicides, new route, synthesis.

## INTRODUCTION

Picoxystrobin (**1**, Figure 1) belongs to the group of strobilurin compounds, which delivers a breadth of spectrum and level of activity on cereals that is superior to other current commercial strobilurin fungicides.[1] It has moderate uptake into host leaves through the xylem and exhibits translaminar movement. Picoxystrobin (**1**) was first developed by Syngenta but is now commercialized by Dupont with the trade name Aproach.[2] Several synthetic methods of picoxystrobin (**1**) have been disclosed by Zeneca (the predecessor of Syngenta).[3–6] However, these methods suffer from several drawbacks such as use of toxic or highly volatile reagent: $Me_2SO_4$, $CCl_4$ and $HCO_2Me$ (Bp: 32 $^oC$), separation by chromatography for several steps as well as low total yield., Herein we describe a new manufacturing route to picoxystrobin (**1**) to expand its application.

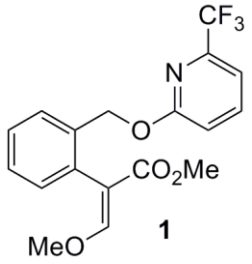
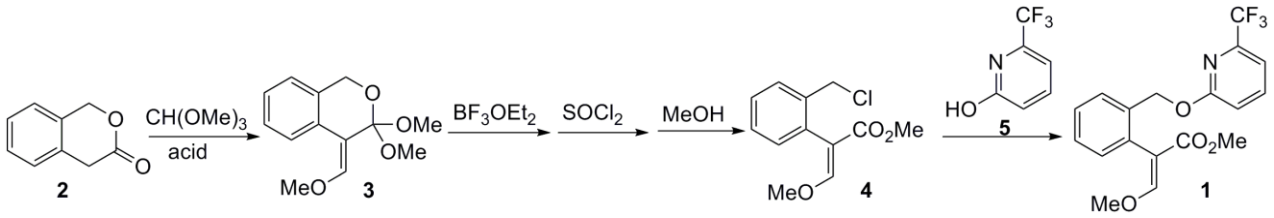



**Figure 1.** Picoxystrobin (**1**).

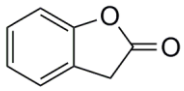
## RESULTS AND DISCUSSION

A novel process is shown in Scheme 1, making it possible to avoid drawbacks of the previous methods. This process started from **2**, and none of the intermediates were needed for separation.

**Scheme 1. The whole process to the synthesis of 1**




The original plan was to transform compound **2** to compound **16** directly. In order to shorten the reaction steps and avoid the highly volatile or toxic reagent ($HCO_2Me$, $Me_2SO_4$), we firstly chose widely used $CH(OMe)_3$ as the reagent. However, to our surprising, $CH(OMe)_3/Ac_2O$, which were efficient reagents for 2(3H)-benzofuranone (Figure 2) in the synthesis of azoxystrobin,[7] proved very poor for **2**. As can be seen from Table 1 and Scheme 2, **16** was hardly produced in the presence of anhydrides such as acetic anhydride or isobutyric anhydride, two effective anhydrides for azoxystrobin[7] (Table 1, entries 1–5).



2(3H)-benzofuranone

**Figure 2.** 2(3H)-benzofuranone.

**Scheme 2. The reaction of 2 with $CH(OMe)_3$ in the presence of anhydrides**

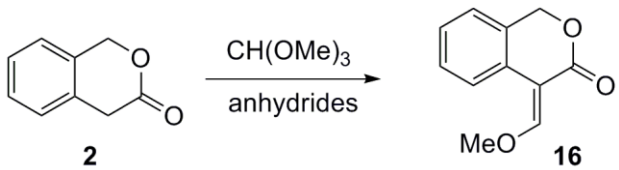


**Table 1. The reaction of 2 with $CH(OMe)_3$ in the presence of anhydrides**[a]

| Entry | $CH(OMe)_3$ | Anhydrides | Yield[b] |
|---|---|---|---|
| 1 | 2.0 equiv | acetic anhydride (8.0 equiv) | <5%[c] |
| 2 | 8.0 equiv | acetic anhydride (2.0 equiv) | <5%[c] |
| 3 | 15.0 equiv | acetic anhydride (5.0 equiv) | <5%[c] |
| 4 | 15.0 equiv | isobutyric anhydride (5.0 equiv) | <5%[c] |
| 5 | 5.0 equiv | acetic anhydride (5.0 equiv) | -[c, d] |

[a]All reactions were carried out both at room temperature and at refluxed temperature equipped with Dean-Stark apparatus for 48 h. [b]Isolated yield. [c]**2** was recovered in more than 95% yield. [d]The reaction was carried out in various solvent such as toluene, DCM, $CH_3CN$, THF.

This great difference between **2** and 2(3H)-benzofuranone, which has one less carbon than **2**, attracted our attention and compelled us to explore it. At the beginning, the reaction, which was catalyzed by Lewis acid, was evaluated, and good results were expected. $BF_3OEt_2$ was first chosen to test the reaction in various solvents. From Table 2, we can see that toluene, THF and DMF were unable to facilitate the reaction, and compound **2** was recovered largely (Table 2, entries 1–3). Compound **16**[8] was the main product when DCM was used as the solvent in spite of the lower yield (Table 2, entry 4). $CH_3CN$ seemed to be useful for the formation of compound **15**[9] (Table 2, entry 5). No good results were obtained with these solvents, so the next reaction was conducted in $CH(OMe)_3$ alone, which acted as both reagent and solvent. The yield of **16** was found similar to that in DCM (Table 2, entry 6). After simple screening for the amount, 10 equiv of $CH(OMe)_3$ proved to be the best for compound **16**, and more compound **15** was formed in the presence of more $CH(OMe)_3$ (Table 2, entries 7–8). The yield was not improved even though the reaction time was prolonged to 48 h at room temperature (Table 2, entry 9). Surprisingly, orthoformate **3** was produced largely when the reaction was heated (Table 2, entries 10–11). Nevertheless, the yield dropped at much higher temperature, such as 80°C, probably due to the

instability of $CH(OMe)_3$ in the presence of Lewis acid catalysts at that temperature (Table 2, entry 12). Luckily, we found that the reaction proceeded quite well when MeOH was used as the solvent. The maximum of 90% yield was reached even at lower temperature (40 $^oC$) without any starting material **2** (Table 2, entries 13–14).

**Scheme 3. The reaction of 2 with $CH(OMe)_3$ catalyzed by $BF_3OEt_2$**

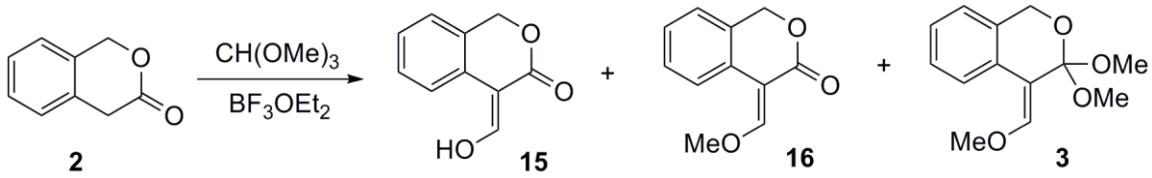



**Table 2. The reaction of 2 with $CH(OMe)_3$ catalyzed by $BF_3OEt_2$**[a]

| Entry | $CH(OMe)_3$ (equiv) | Solvent | Temp (°C) | Yield (%)[b, c] |
|---|---|---|---|---|
| 1 | 5.0 | Toluene | 25 | **15**: 0%, **16**: <5%, **3**: 0% |
| 2 | 5.0 | THF | 25 | **15**: 0%, **16**: <5%, **3**: 0% |
| 3 | 5.0 | DMF | 25 | NR |
| 4 | 5.0 | DCM | 25 | **15**: trace, **16**: 18%, **3**: 0% |
| 5 | 5.0 | $CH_3CN$ | 25 | **15**: 13%, **16**: 8%, **3**: 0% |
| 6 | 5.0 | - | 25 | **15**: trace, **16**: 19%, **3**: 0% |
| 7 | 10.0 | - | 25 | **15**: 4%, **16**: 32%, **3**: 0% |
| 8 | 15.0 | - | 25 | **15**: 8%, **16**: 30%, **3**: 0% |
| 9 | 10.0 | - | 25[d] | **15**: 6%, **16**: 33%, **3**: 0% |
| 10 | 10.0 | - | 40 | **15**: trace, **16**: 23%, **3**: 41% |
| 11 | 10.0 | - | 60 | **15**: 0%, **16**: 24%, **3**: 58% |
| 12 | 10.0 | - | 80 | **15**: 0%, **16**: 8%, **3**: 44% |
| 13 | 10.0 | MeOH | 40 | **15**: 0%, **16**: 0%, **3**: 90% |

| | | | | |
|---|---|---|---|---|
| 14 | 10.0 | MeOH | 30 | **15**: 0%, **16**: 10%, **3**: 75% |

[a]All reactions were carried out with **2** (0.01 mol) catalyzed by 0.5 eq $BF_3OEt_2$ for 24 h. 10 mL solvent was used if necessary. [b]Isolated yield. [c]No other evident compounds except for the listed were found. [d]The reaction time was 48 h.

Next, the amount of $BF_3OEt_2$ was screened, and the results are listed in Scheme 4 and Table 3. Decreasing the amount of $BF_3OEt_2$ resulted in a lower yield of **3**, for example only 48% of **3** was obtained when there was only 0.1 equiv of $BF_3OEt_2$ (Table 3, entry 1). The main reason for this low yield was the low transformation of **2** (20–40% was recovered) catalyzed by a small amount of $BF_3OEt_2$. It is unnecessary to use more $BF_3OEt_2$, such as 1.0 equiv, which gave similar result to 0.5 equiv (Table 3, entry 3). As expected, nothing happened when no catalyst was added (Table 3, entry 4). Other common Lewis acids, such as $TiCl_4$ and $AlCl_3$, produced only **16** in less than 20% yield without **3**.

**Scheme 4. Comparison of the amount of $BF_3OEt_2$ for the formation of 3**

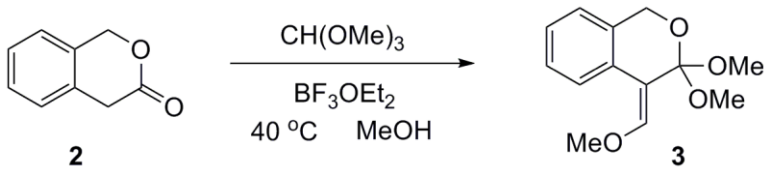


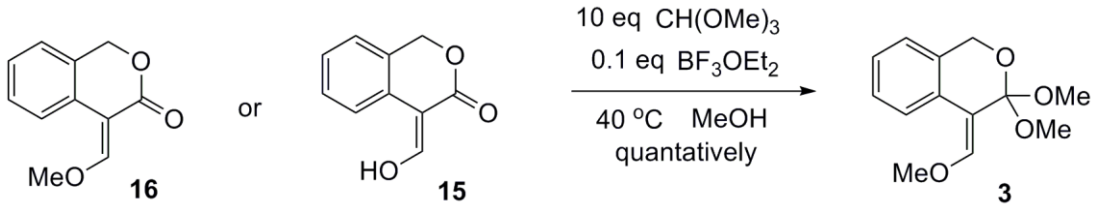

**Table 3. Comparison of the amount of $BF_3OEt_2$ for the formation of 3[a]**

| Entry | Lewis acid | Equiv | Yield of **3**[b] |
|---|---|---|---|
| 1 | $BF_3OEt_2$ | 0.1 | 48%[c] |
| 2 | $BF_3OEt_2$ | 0.2 | 71%[c] |
| 3 | $BF_3OEt_2$ | 1.0 | 90% |
| 4 | - | - | -[d] |

[a]All reactions were carried out with 10 equiv of $CH(OMe)_3$ in MeOH at 40 °C for 24 h. [b]Isolated yield. [c]**2** was recovered in 20–40 yields. [d]No reaction happened and **2** was recovered completely.

The intermediate was considered likely to be compound **16** or **15**. It was heated with $CH(OMe)_3$ and $BF_3OEt_2$ independently. It was clear that **16** or **15** was easy to be transformed to **3**, with $CH(OMe)_3$ even when 0.1 equiv of $BF_3OEt_2$ was used (Scheme 5).

**Scheme 5. The formation of 3 through 16 or 15**




Several proton acids were also examined (Table 4). TsOH exhibited the best activity among these proton acids. For others such as TFA and HOAc, **16** was obtained only in less than 25% without **3** even when the reaction was allowed to run for 72 h at reflux. For this reason, after the screening, $BF_3OEt_2$ was concluded to be the best catalyst for this reaction.

**Table 4. The reaction of 2 with $CH(OMe)_3$ catalyzed by proton acid[a]**

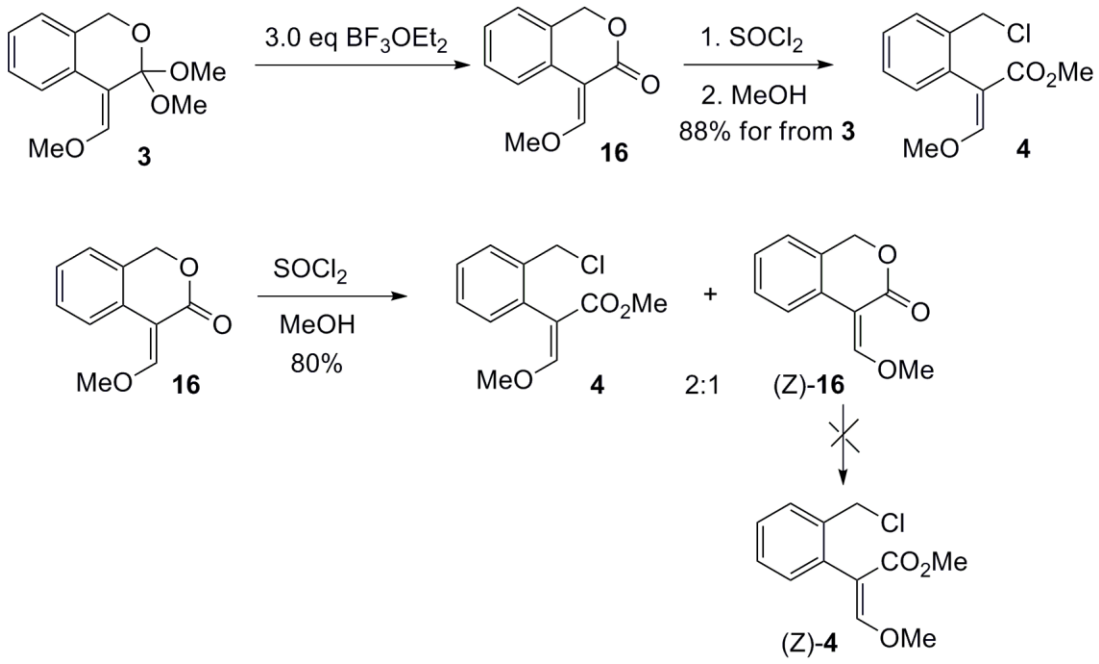
| Entry | Proton acid | Temp (°C) | Time (h) | Yield[b] |
|---|---|---|---|---|
| 1 | TFA(0.5 to 3.0 equiv) | 40[c] or refluxed[d] | 24 | **3**: 0%, **16**<10%[e] |
| 2 | HOAc(0.5 to 3.0 equiv) | 40[c] or refluxed[d] | 36–72 | **3**: 0%, **16**: 5–25%[e] |
| 3 | TsOH (0.5 equiv) | 40[c] | 24 | **3**: 65%, **16**: 0%[e] |

[a]All reactions were carried out in 10 equiv of $CH(OMe)_3$. [b]Isolated yield. [c]MeOH was added [d]MeOH was not added. [e]**2** was mainly recovered.

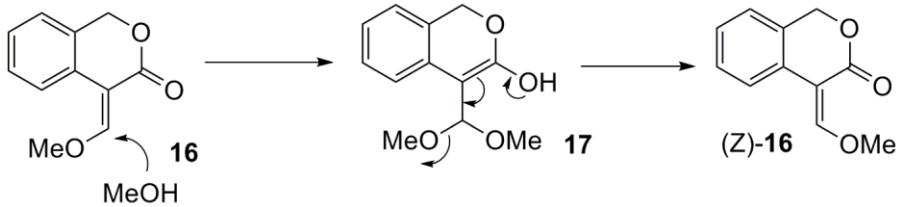
With **3** in hand, we then tried to synthesize **4** through ring-opening reaction. It was found that **3** could be easily converted back to **16** in the presence of excessive $BF_3OEt_2$ (3.0 equiv) after distillation of $CH(OMe)_3$ and MeOH. Compound **4** was then formed smoothly when the reaction was carried out step-wisely. MeOH was mixed after the reaction of **16** with $SOCl_2$ was finished

to produce **4** in 88% from **3**. This compound was used for the next step without purification. It is very interesting that Z-form of compound **16** was formed along with **4** when $SOCl_2$ was added to **16** in MeOH. Unlike **16**, (Z)-**16** remained unchanged, once it was formed (Scheme 6). The structure of (Z)-**16** was identified by NMR and MS(EI), and compared to that of **16**.[8, 10] The possible course for the formation of (Z)-**16** was postulated as described in Scheme 7.

**Scheme 6. Synthesis of 4**




**Scheme 7. Postulated course for the formation of (Z)-16**




The final step was the coupling reaction of **4** with **5** to construct the ether bond. The base was found to be the key factor. Different bases were screened for this reaction, and the results are

listed in Table 5. As shown, no product was observed by organic base such as $Et_3N$, DIPEA or pyridine in different solvents (Table 5, entries 1–3). On the contrary, inorganic base showed good activity, either $Na_2CO_3$, $K_2CO_3$ or NaOH, KOH gave desired product **1** in different yields at elevated temperature (Table 5, entries 4–7). Finally, the reaction temperature and the solvent were evaluated after $K_2CO_3$ was selected as the base. It could be seen that the yield was negatively influenced by both higher and lower temperature (Table 5, entries 8–9). Besides, other solvents, such as THF and toluene, were proved to be inferior to DMF (Table 5, entries 10–11).

**Scheme 8. Synthesis of 1**

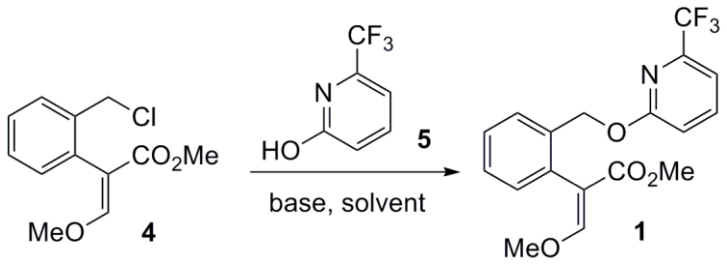



**Table 5. Condition screening for synthesis of 1**[a]

| Entry | Base | Solvent | Yield[b] |
|---|---|---|---|
| 1 | $Et_3N$ | DMF or THF or tol | NR |
| 2 | DIPEA | DMF | NR |
| 3 | Pyridine | DMF | NR |
| 4 | $Na_2CO_3$ | DMF | 80% |
| 5 | $K_2CO_3$ | DMF | 95% |
| 6 | NaOH | DMF | 79% |
| 7 | KOH | DMF | 80% |
| 8 | $K_2CO_3$ | DMF | 15–86%[c] |
| 9 | $K_2CO_3$ | DMF | 88%[d] |

| | | | |
|---|---|---|---|
| 10 | $K_2CO_3$ | Tol | NR |
| 11 | $K_2CO_3$ | THF | 54% |

[a]All reactions were carried out with **4** (0.05 mol), **5** (1.3 equiv) and base (2.0 equiv) in solvent at 70 °C for 24 h. [b]Isolated yield. [c]The reaction was carried out at 30–60 °C. [d]The reaction was carried out at 80 °C.

## CONCLUSION

A new and efficient manufacturing technology was developed for the preparation of picoxystrobin (**1**). Isochromanone (**2**) was used as the stating material which was transformed to **3** catalyzed by acid catalyst such as $BF_3OEt_2$. **1** was finally obtained after ring-opening and coupling reaction. In this process, routinely used reagents were employed and all the intermediates could be used directly for the next step without purification.

## EXPERIMENTAL SECTION

**General.** Melting points were recorded on an RY-1 melting point apparatus and were uncorrected. $^1H$ (400 MHz) and $^{13}C$ (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standards. J values were given in hertz. Mass spectra were recorded on a Finnigan MAT-95/711 spectrometer. HPLC analysis was performed by a standard method on a Diamonsil $C_{18}$ column, 250 mm × 4.6 mm (5 μm); λ = 210 nm; mobile phase: A ($CH_3CN$) and B ($H_2O$), 70:30 v/v. The HPLC analysis data is reported in area % and is not adjusted to weight %.

**(E)-3, 3-dimethoxy-4-(methoxymethylene)isochroman (3).** To a stirred solution of **2** (592.5 g, 4.0 mol) and $CH(OMe)_3$ (4.24 kg, 40.0 mol) in MeOH (4 L) was added $BF_3OEt_2$ (284.0 g, 2.0 mol) at 25 °C. Then the mixture was stirred for 24 h at 40 °C. After concentration of $CH(OMe)_3$

and MeOH, crude **3** (P: 90%) was used directly for next step. A sample of purified **3** as pale-yellow oil was analyzed as follows: $^{1}$H NMR($CDCl_3$, 400 MHz): $\delta$ = 3.30 (s, 3H), 3.68 (s, 3H), 3.79 (s, 3H), 4.34 (s, 2H), 7.12 (dd, $J$ = 0.8, 7.2 Hz, 1H), 7.25−7.32 (m, 2H), 7.46 (t, $J$ = 7.2 Hz, 1H), 7.55 (s, 1H); $^{13}$C NMR($CDCl_3$, 100 MHz): $\delta$ = 51.4, 58.0, 61.7, 72.2, 110.3, 127.1, 127.5, 127.8, 130.8, 131.5, 137.4, 159.8, 167.9; ESI-MS (*m/z*) 259 $[M + Na]^+$.

**(E)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxyacrylate (4).** The mixture of crude **3** from last step in $BF_3OEt_2$ (1.53 kg, 10.8 mol) was heated for 2 h at 50 $^{o}$C. After distillation of $BF_3OEt_2$, the residue was refluxed in $SOCl_2$ (2.14 kg, 18.0 mol) for 24 h. After $SOCl_2$ was eliminated, the liquid mixture was added dropwise to MeOH (5.76 kg, 180.0 mol) at 25 $^{o}$C and stirred for 2 h at that temperature. After MeOH was evaporated, sat $NaHCO_3$ aq (5 L) and DCM (2 L) was added. The separated water layer was extracted with DCM (2 L). The combined organic layer was washed with water (2 L), dried with anhydrous $Na_2SO_4$, filtered and concentrated to afford **4** (812.0 g) as yellow oil. Crude **4** was used directly for next step. A sample of purified **4** as off-white solid was analyzed as follows: Mp: 94~95 $^{o}$C. $^{1}$H NMR($CDCl_3$, 400 MHz): $\delta$ = 3.70 (s, 3H), 3.79 (s, 3H), 4.50 (s, 2H), 7.14−7.17 (m, 1H), 7.32−7.34 (m, 2H), 7.49−7.51 (m, 1H), 7.62 (s, 1H); $^{13}$C NMR($CDCl_3$, 100 MHz): $\delta$ = 44.5, 51.7, 62.0, 109.7, 128.32, 128.34, 129.6, 131.3, 132.4, 136.4, 160.5, 167.8; ESI-MS (*m/z*) 263, 265 $[M + Na]^+$.

**Picoxystrobin (1).** The mixture of crude **4** from last step, **5** (672.0 g, 4.12 mol) and $K_2CO_3$ (875.0 g, 6.34 mol) in DMF (5 L) was stirred at 70 $^{o}$C for 24 h. EtOAc (10 L), water (6 L) and brine (6 L) was subsequently added to the mixture. The aqueous layer was extracted with EtOAc (3 × 3 L) after separation. The combined organic layer was concentrated after washed with brine (10 L) and dried with anhydrous $Na_2SO_4$ to give an oil, which was dissolved in MeOH (600 mL)

at 60 °C. An off- white solid precipitated when the mixture was cooled to 5 °C, then standing at -15 °C. This solid was filtered, washed with hexane (800 mL), and dried at 40 °C under vacuum to afford **1** (1 kg, 68% from **2**) as a white solid with 99% purity by HPLC (retention time: 9.1 min). Mp: 74–75 °C (lit. mp 73–74).[3a] $^1$H NMR($CDCl_3$, 400 MHz): $\delta$ = 3.57 (s, 3H), 3.68 (s, 3H), 5.25 (s, 2H), 6.78 (d, $J$ = 8.4 Hz, 1H), 7.08−7.14 (m, 2H), 7.23−7.25 (m, 2H), 7.45−7.48 (m, 2H), 7.56 (t, $J$ = 8.0 Hz, 1H); $^{13}$C NMR($CDCl_3$, 100 MHz): $\delta$ = 51.5, 61.8, 66.3, 110.2, 113.3 (d, $J$ = 2.8 Hz), 114.7, 121.4 (d, $J$ = 272.7 Hz), 127.8, 127.9, 128.8, 131.1, 132.3, 135.7, 139.4, 145.3 (q, $J$ = 35.3 Hz), 159.9, 163.6, 168.0; ESI-MS (*m/z*) 390 $[M + Na]^+$. The data conforms to that described in known publication.[3a]

**(Z)-4-(methoxymethylene)isochroman-3-one Z-(16).** To a stirred solution of **3** (5.0 g, 21.2 mmol) in MeOH (6.8 g, 212.0 mmol) was added $SOCl_2$ (10.1 g, 84.8 mmol) at 25 °C. Then the mixture was stirred for 24 h at 40 °C. After concentration, water (50 mL) was added and extracted with DCM (2×50 mL). The combined organic layer was washed with brine (100 mL), dried with anhydrous $Na_2SO_4$, filtered and concentrated to afford yellow oil. **Z-(16)** was purified via silica gel column chromatography using EtOAc/hexane (1:10) as eluent to yield 0.99 g (25%) as light-yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3H), 5.12 (s, 2H), 7.01 (d, $J$ = 7.2 Hz, 1H), 7.21 (dt, $J$ = 1.2, 7.2 Hz, 1H), 7.31 (dt, $J$ = 1.2, 7.6 Hz, 1H), 7.71 (s, 1H), 8.10 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 51.2, 69.3, 109.2, 123.6, 123.9, 126.6, 127.2, 127.5, 128.6, 157.5, 166.0; EI-MS m/z: 190 ($M^+$, 85.21), 135 (100), 118 (44.69), 90 (35.15), 77 (50.65).

ASSOCIATED CONTENT

**Supporting Information**.

$^{1}H$ and $^{13}C$ NMR spectra.

AUTHOR INFORMATION

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**Notes**

The authors declare no competing financial interest.

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5. (a) Stilbene Derivatives, and Fungicides which Contain These Compounds. Schirmer, U.; Karbach, S.; Pommer, E. H.; Ammermann, E.; Steglich, W.; Schwalge, B. A. M.; Anke, T. U. S. patent 4723034, 1987; CAN 106:101890. (b) Fungicides. Clough, J. M.; Godfrey, C. R. A.; De Fraine, P. J.; Hutchings, M. G.; Anthony, V. M. E. P. patent 278595, 1988; CAN 109:210725.

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7. Process for the Preparation of Pyrimidine Compounds. Jones, J. D.; Deboos, G. A.; Wilkinson, P.; Cox, B. G.; Fielden, J. M. W. O. patent 9208703, 1992; CAN 117:131219.

8. A sample of **16** as an off-white solid purified by column chromatography was analyzed as follows: Mp: 89.5–90.5 $^{o}$C. $^{1}$H NMR($CDCl_3$, 400 MHz): δ = 4.03 (s, 3H), 5.24 (s, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* =7.2 Hz, 1H), 7.73 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR($CDCl_3$, 100 MHz): $\delta$ = 63.1, 69.1, 103.3, 123.9, 126.2, 126.6, 127.9, 128.90, 128.93, 160.8, 168.4; EI-MS m/z: 190 ($M^+$, 100), 135 (34.18), 118 (70.83), 90 (46.04), 77 (31.15).

9. A sample of **15** as a yellow solid purified by column chromatography was analyzed as follows: Mp: 105–106 $^{o}$C. $^{1}$H NMR($CDCl_3$, 400 MHz): δ = 5.30 (s, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.15 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.22-7.25 (m, 1H), 7.25-7.29 (m, 1H), 7.86 (d, *J* = 7.6 Hz, 1H); 12.38 (d, *J* = 12.8 Hz, 1H). The data conforms to that described in known publication.[6]

10. EI-MS was specially run to obverse the fragment peaks for the comparison of (Z)-**16** with **16**. For details, please see experimental section.