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Efficient synthesis of azoxystrobin and its key intermediate using a newer DABCO-based catalyst

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RESEARCH ARTICLE

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ABSTRACT

A simple, convenient, and commercially feasible synthesis method has been developed for the synthesis of azoxystrobin and its intermediate using a DABCO-based catalyst. The methodology, which starts with coumaranone, uses a single catalyst for the two-step process, demonstrating high potential for industrial application. The catalyst synthesis and optimal catalyst concentration have been optimized to achieve maximum yield in the synthesis of the intermediate as well as technical azoxystrobin. The intermediate and final products, as well as the catalyst, were characterized by melting point, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry. The HRMS analysis data supported the molecular formulae of the synthesized catalyst and product, showing the fragments *m/z* 143.1188 (M+H), $C_7H_{14}N_{20}$ and 404.1262 (M+H), $C_{22}H_{17}N_3O_5$. The newer catalyst has the merits of being inexpensive, highly reactive, and environmentally friendly. The yield reached a high level, and this method can be considered a promising catalyst for the industrial-scale production of azoxystrobin and its key intermediate.

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1. Introduction

In the fungicide market, strobilurin molecules play a vital role and are used in foliar applications and crop treatments. These categories of fungicides are known for their characteristic inhibition of mitochondrial respiration in target organisms, as a result of this, an interruption occurs in their energy production [1]. The strobilurin group of chemicals is known to be effective in controlling wide range of fungal diseases. Strobilurin fungicides are mainly used to control rust, powdery mildew, and various leaf spots diseases. Their broad spectrum activity makes them a widely used to ensure healthy plants [2]. Along with these advantages, there are some drawbacks that arise due to the overuse of strobilurin fungicide, including the development of resistance to fungicides in some pathogen populations. To avoid this drawback, careful management and strategies are needed in agricultural practices. In a contemporary scenario, the strobilurins class of fungicides provides a critical support in enhancing crop yields, which is very essential for fulfilling the need for an increasing population. This pivotal role of Azoxystrobin is only due to its broad-spectrum fungicidal activity [3,4]. The notable members of the strobilurin family that have a broad spectrum of activity are azoxystrobin, picoxystrobin, trifloxystrobin, and fluoxastrobin.

Researchers have explored numerous methods for synthesizing azoxystrobin (Figure 1). Syngenta, as an inventor, and others contributed to the reporting of a range of approaches [5-10]. The most common route begins with 2-hydroxyphenylacetic acid, an industrial raw material, which is converted into the intermediate methyl-2-(2-hydroxy phenyl)-3,3-dimethoxypropanoate [11-14]. A key stage in the process is the cross-coupling of *(E)*-methyl-2-[2-(6-chloro pyrimidin-4-yloxy) phenyl]-3-methoxyacrylate with 2-cyano phenol.

Different techniques have been documented for this step. For example, Ullmann coupling using copper catalysts is performed at temperatures above 100 °C [15]. Other reports describe catalyst-free and solvent-free reactions at slightly higher temperatures, above 110 °C [16–18].

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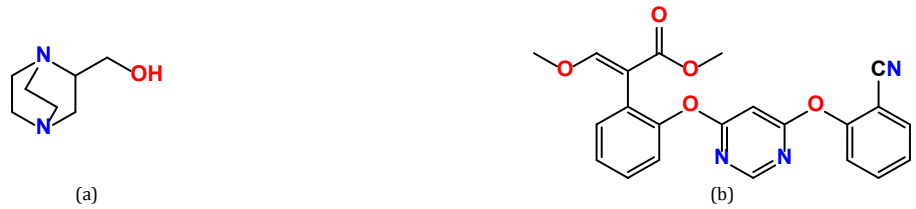
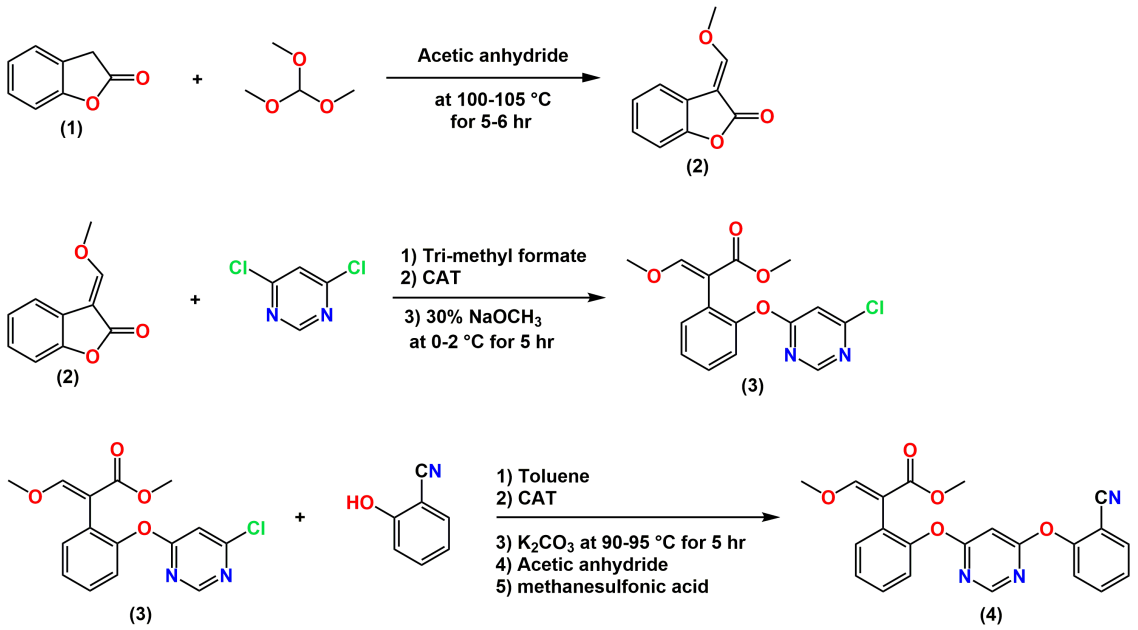


Figure 1. Structures of (a) catalyst (CAT) and (b) azoxystrobin.



Scheme 1. Azoxystrobin synthesis protocol by using CAT.

Another option involves nucleophilic substitution with 1,4-diazabicyclo[2.2.2]octane (DABCO) (Figure 1), performed in solvents such as DMF, DMSO or even xylene [19,20].

All of these reported methods have their own set of challenges. For example, some methods require high temperatures, which is energy intensive and increases the probability of bioproducts, while others may not produce the best yields [21-24]. In some processes, there are issues with how well substances mix due to heterogeneous reagents, plus some techniques need special equipment and complicated processes to clean afterward [24]. Take DABCO, for example, it is great for achieving high yields [25,26], but its expensive nature makes it difficult for many to use it regularly.

To streamline the process, it is generally recommended to construct the methyl α-phenyl-β-methoxyacrylate fragment early, before assembling the central pyrimidinyloxy ring and the terminal cyanophenoxy group. In a typical synthetic pathway, *(E)*-methyl-2-(2-hydroxyphenyl)-3-methoxyacrylate is reacted with 4,6-dichloropyrimidine in an alkaline medium, often using *N*,*N*-dimethylformamide. This produces *(E)*-methyl-2-[2-(6-chloropyrimidin-4-yloxy)phenyl]-3-metho xyacrylate, which can then undergo an Ullmann-type coupling with 2-cyanophenol to obtain the desired product [21]. Despite extensive research on the development of synthetic pathways for azoxystrobin, challenges persist in its industrial application. Scheme 1 represents a fundamental three-step synthetic route to azoxystrobin.

Intermediate and final products obtained using previously reported methods for azoxystrobin synthesis exhibit relatively low yields (75%) and moderate purities (95-97%) [22,23]. Therefore, more efficient, scalable, and cost-effective synthetic approaches are required.

In this study, we present a new DABCO-based catalyst (CAT) ((1,4-diazabicyclo[2.2.2]octan-2-yl)methanol) (Figure 1) to address the ongoing problems in industrial production, which may effectively catalyze the aromatic nucleophilic substitution of the pyrimidine ring, resulting in the preparation of azoxystrobin (Scheme 1). This attractive catalyst was prepared from piperazine (Scheme 2) and characterized using various spectroscopic techniques. This catalyst is of great importance because it is used in two consecutive steps for azoxystrobin synthesis with low consumption.

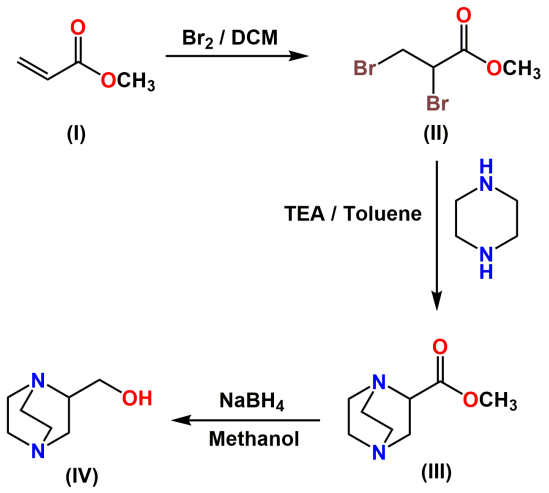
2. Experimental

2.1. Materials and instrumentation

The chemicals and reagents used in this study were purchased from Sigma-Aldrich and TCI and were used without additional purification. The solvents were subjected to distillation and dried to remove moisture prior to use. Reactions were monitored using thin layer chromatography (TLC) with Merck silica gel 60 F_{254}, and visualization was performed in UV light at 254 and 365 nm. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS) using a Waters Q-TOF micromass spectrometer. NMR spectra were recorded in $CDCl_3$ on a Bruker AC-500 MHz spectrophotometer with tetramethylsilane (TMS) serving as internal reference standard.

2.2. Synthesis

2.2.1. Synthesis of catalyst



Scheme 2. Synthesis of (1,4-diazabicyclo[2.2.2]octan-2-yl)methanol (CAT).

(1,4-Diazabicyclo[2.2.2]octan-2-yl)methanol was synthesized in three stages. In stage I, bromination, methyl acrylate was formed in the DCM solvent, while in stage II, dibromomethyl propionate was reacted with piperazine to obtain methyl 1,4-diazabicyclo[2.2.2]octane-2-carboxylate as ester product. In the final stage, the ester group was reduced to alcohol (1,4-diazabicyclo [2.2.2]octan-2-yl)methanol using sodium borohydride in a methanol solvent with excellent yield.

2.2.1.1. Synthesis of methyl 2,3-dibromopropanoate (II)

Methylacrylate (I) (8.6 g, 0.1 mol) in DCM (25 mL) was loaded to a 100 mL round bottom flask and bromine (20 g, 0.12 mol) was added at 28-30 °C for 1 h. The reaction progress was monitored by TLC. The resulting brown solution was treated with an aqueous solution of sodium metabisulfite to destroy excess bromine. The organic layer was washed with water until the pH was neutral and dried over anhydrous Na_2SO_4. The solvent was recovered under vacuum to obtain yellow oil (II), Yield: 94-95%.

2.2.1.2. Synthesis of methyl 1,4-diazabicyclo[2.2.2]octane-2-carboxylate (III)

The mixture of methyl 2,3-dibromopropanoate (II) (12.3 g, 0.05 mol), triethylamine (11.2 g, 0.11 mol) and piperazine (4.8 g, 0.055 mol) in toluene (50 mL) was heated at 85-90 °C for 2-4 h. The reaction was monitored by TLC to check for unreacted II; After the reaction, the mass was quenched in cold water and the organic layer was washed with water to neutral pH and dried with anhydrous Na_2SO_4. The solvent was recovered under vacuum to obtain a pale yellow solid. Yield: 80-82%, the obtained product (III) was used further without purification.

2.2.1.3. Synthesis of (1,4-diazabicyclo[2.2.2]octan-2-yl) methanol (IV)

A solution of methyl-1,4-diazabicyclo[2.2.2]octane-2-carboxylate (III) (7.2 g, 0.05 mol) and methanol (35 mL) was loaded into a 100 mL round bottom flask and $NaBH_4$ (3.8 g, 0.1 mol) was added lot-wise at 10-15 °C for 2-3 h. The reaction mixture was maintained at 25-30 °C for 2-4 h. The reaction progress was monitored by TLC. The resulting solution was treated with an aqueous solution of ammonium chloride. The solvent was recovered under vacuum to obtain a dark yellowish-brown mass, and the product was extracted with ethyl acetate. The solvent was recovered under vacuum to obtain a pale yellow solid, the obtained product (IV) was purified by column chromatography.

(1,4-Diazabicyclo[2.2.2]octan-2-yl)methanol (IV): Color: Off white solid. Yield: 60%. M.p.: 71-72 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 2.23 (d, *J* = 7.65 Hz, 1H, -C*H*$_2$-CH), 2.56-2.95 (m, 10H, -C*H*$_2$-CH-,-C*H*$_2$-N-, -N-C*H*-CH$_2$), 3.46 (d, *J* = 6.9 Hz, 1H, -C*H*$_2$-OH), 3.60 (d, *J* = 6.9 Hz, 1H, -C*H*$_2$-OH), 4.16 (s, 1H, -CH$_2$-O*H*). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 40.5, 46.8, 49.6, 56.4, 61.7, 63.3 68.0. HRMS *m/z* calculated for $C_{18}H_{29}N_2O$: 142.1106, found: 143.1188 $[M+H]^+$.

2.2.2. Synthesis of azoxystrobin

Azoxystrobin was synthesized in three steps. In the first step, *(E)*-3-(methoxymethylene)benzofuran-2(3*H*)-one (2) was synthesized from 2-coumaranone (1), while *(E)*-2-(2-((6-chloropyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (3) was synthesized using CAT in a methyl formate solvent. Finally, the desired product azoxystrobin (4), was synthesized in the third step, using a new catalyst (CAT).

2.2.2.1. Synthesis of (E)-3-(methoxymethylene)benzofuran-2(3H)-one (2)

The mixture of 2-coumaranone (1) (13.4 g, 0.1 mol), trimethyl orthoformate (15.9 g, 0.16 mol) and acetic anhydride (31 g, 0.3 mol) in a 100 mL round bottom flask was heated to reflux (100-105 °C) for 5-6 h. Monitored the reaction using the TLC method to verify unreacted 2-coumaranone; after the reaction was completed, the generated acetic acid and methyl acetate under reduced pressure. The residual mass was then quenched in cold water, and the product was extracted with toluene. The organic layer was washed with a 5% $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvent was recovered under vacuum to obtain a pale yellow solid, Yield: 84-85%, and the pure product (2) was obtained by repurification in toluene solvent.

(E)-3-(Methoxymethylene)benzofuran-2(3H)-one (2): Color: Pale yellow solid. M.p.: 102-104 °C. Yield: 85%. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.11 (s, 3H, -CH-OC*H*$_3$), 7.04 (d, *J* = 7.95 Hz, 1H, Ar-*H*), 7.08-7.11 (t, *J* = 7.55 Hz, 1H, Ar-*H*), 7.20-7.23 (t, *J* = 7.61 Hz, 1H, Ar-*H*), 7.54 (d, *J* = 1.25 Hz, 1H, Ar-*H*), 7.56 (s, 1H, -C=C*H*-OCH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 169.62, 160.03, 151.55, 127.9, 123.6, 122.75, 122.46, 110.05, 103.41, 63.65.

Table 1. Effects of the mole ratio of catalyst (CAT) on the yields of compound 3.

Entry	CAT (IV) in equiv.	Isolated yield in %
1	0.010	72
2	0.015	76
3	0.020	80
4	0.025	80
5	0.030	80

Table 2. Effects of the mole ratio of catalyst (CAT) on the yields of compound 4.

Entry	CAT (IV) in equiv.	Isolated yield in %
1	0.020	90
2	0.025	92
3	0.050	96
4	0.075	97
5	0.100	97

2.2.2.2. Synthesis of methyl (E)-2-(2-((6-chloropyrimidin-4-yl) oxy) phenyl)-3-methoxyacrylate (3)

The mixture of compound (2) (17.6 g, 0.1 mol) and 4,6-dichloropyrimidine (17.9 g, 0.12 mol) in methyl formate solvent (20 mL) was cooled to 0-2 °C. Upon cooling, the simultaneous dropwise addition of CAT (0.28 g, 0.002 mol) and 30% $NaOCH_3$ methanolic solution (22.5 g, 0.125 mol) was carried out for 5-6 h. Increased the temperature and maintained the reaction mixture for 4-5 h at 9-12 °C. The reaction mixture was monitored by TLC to check the unreacted dichloropyrimidine; after the reaction was complete, the pH of the reaction mixture was adjusted to 6.0-6.5, using acetic acid. The reaction mixture was quenched in cold water and the product was extracted with toluene. The organic layer was washed with cold water until the pH was neutral and dried over anhydrous Na_2SO_4. The dehydrated toluene layer was further treated with acetic anhydride (9.5 g, 0.09 mol) using methane sulfonic acid (0.48 g, 0.005 mol) as catalyst at 70-75 °C for 2-4 h, to convert the intermediate into the target product (3). Finally, the reaction mixture was quenched in cold water, and the product was extracted with toluene. The toluene layer was washed to neutral pH, the solvent was recovered under vacuum to obtain yellow solid. The product was further recrystallized from methanol solvent.

Methyl (E)-2-(2-((6-chloropyrimidin-4-yl) oxy) phenyl)-3-methoxyacrylate (3): Color: Pale yellow solid. Yield: 80%. M.p.: 103-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.59 (s, 3H, -C(O)-OC*H*$_3$), 3.72 (s, 3H, -CH-OC*H*$_3$), 6.78 (s, 1H, Ar-*H*), 7.16 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.29 (d, *J* = 7.67 Hz, 1H, Ar-*H*), 7.32-7.35 (t, *J* = 6.83 Hz, 1H, Ar-*H*), 7.38-7.41 (t, *J* = 6.65 Hz, 1H, Ar-*H*), 7.44 (s, 1H, -C=C*H*-OCH_3), 8.57 (s, 1H, -N-C*H*-N). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 51.56, 61.95, 106.94, 107.24, 121.91, 125.92, 126.14, 129.26, 132.81, 149.85, 158.49, 160.64, 161.77, 167.20, 170.30.

2.2.2.3. Synthesis of methyl (E)-2-(2-((6-(2-cyanophenoxy) pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (4)

A mixture of 2-cyanophenol (13.2 g, 0.11 mol), toluene (80 mL) and anhydrous K_2CO_3 (16.7 g, 0.12 mol) was heated at 90-95 °C for 1 h in a 100 mL round bottom flask. After cooling the reaction mixture at 80-85 °C, compound 3 (32.4 g, 0.10 mol) and CAT (0.7 g, 0.005 mol) were added, and the reaction was further maintained at 90-95 ° C for 4-5 hrs. Upon completion, the reaction mixture was quenched with cold water and the layers were separated. The toluene layer was washed with water until a neutral pH was attained. The solvent was removed under reduced pressure to yield a pale-yellow solid. The crude product was recrystallized from methanol to obtain the off-white crystalline compound (4).

Methyl (E)-2-(2-((6-(2-cyanophenoxy)pyrimidin-4-yl)oxy) phenyl)-3-methoxyacrylate (4): Color: Off white solid. Yield: 92-93%. M.p.: 117-118 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.62 (s, 3H, -C(O)-OC*H*$_3$), 3.72 (s, 3H, -CH-OC*H*$_3$), 6.41 (s, 1H, Ar-*H*), 7.20 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.27-7.29 (t, *J* = 8.0 Hz, 2H, Ar-*H*), 7.32 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.37-7.41 (m, 1H, Ar-*H*), 7.49 (s, 1H, -C=C*H*-OCH_3), 7.62-7.66 (m, 1H, Ar-*H*), 7.68 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H, Ar-*H*), 8.39 (s, 1H, -N-C*H*-N). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 51.5, 61.9, 92.4, 106.9, 107.28, 115.2, 122.0, 123.1, 125.8, 126.0, 126.1, 129.1, 132.7, 133.5, 134.2, 150.2, 154.1, 157.9, 160.7, 167.3, 170.1, 171.8. HRMS *m/z* calculated for $C_{22}H_{17}N_3O_5$: 403.1168, found: 404.1262 $[M+H]^+$.

3. Results and Discussion

3.1. Chemistry

To optimize the yield, it is crucial to select the most favorable reaction conditions identified through systemic optimization of the mole ratio of catalyst as given in Tables 1 and 2. A novel catalyst was synthesized through a three-step process that is both straightforward and cost-effective. Table 1 shows the impact of varying the mole ratio of the catalyst on the yield of compound 3. The use of 0.02 equivalents of the catalyst resulted in the highest yield of intermediate 3, reaching up to 80 %. The experimental data clearly indicate that increasing the molar ratio of the catalyst did not affect the yield of compound 3. However, employing half the amount of catalyst, specifically 0.01 equivalents, can reduce the yield to 72%.

Table 2 shows that compound 4 yield can reach 97% when catalyst molar ratio to *(E)*-2-(2-((6-chloropyrimidin-4-yl) oxy) phenyl)-3-methoxyacrylate (3) was maintained at 0.1:1, and reached 96% with half the amount of catalyst. The process was optimized, with the highest yield observed at temperatures ranging from 90-95 °C; at lower temperatures, the reaction did not proceed to completion. Numerous synthesis processes for azoxystrobin have been reported using a DMF solvent, which poses challenges for workup because of its high boiling point and polar nature. Increasing the catalyst loading improved the product formation efficiency. Consequently, we recommend an optimized process that yields 96% with 0.05 equivalent catalyst.

3.2. Plausible mechanism

In the initial stage of compound 3 synthesis, the coumaranone ring in compound 2 was cleaved using a sodium methoxide solution, resulting in the formation of a phenoxy-ester group [23]. The catalyst facilitates an attack on pyrimidine through an addition-elimination mechanism [23]. Subsequently, once formed, the phenoxyester group readily interacted with pyrimidine in the presence of the catalyst at low temperature [23]. Maintaining a low temperature is advantageous for preventing the β-addition of sodium methoxide to the acrylate in compound 2 and to avoid loss of 4,6-dichloro pyrimidine, as sodium methoxide can react with 4,6-dichloro pyrimidine [23] (Figure 2).

Table 3. Comparison of the literature and the present study for the preparation of compound 4.

Catalyst used	Catalyst loading	Time in hr	Temp °C	Solvent	Yield	Reference
Trimethylamine	2%	8	80°C	Toluene	~96.8%	[23]
Azabicyclic compounds	8%	~4	60-100°C	Butyl acetate, toluene, or xylene	~65-70%	[5]
FeO	10%	1.5	120°C	DMF	89%	[8]
DBU/DBN	0.1-5%	7-8	90°C	DMF	High*	[22]
DABCO	0.1-2%	7-8	80°C	DMF	98%	[26]
Crown Ethers or PEG	0.05 -2%	10	80-150°C	Toluene, xylene	97%	[27]
Cu	1-13%	10	95°C	DMF	64-65%	[28]
DABCO-based (CAT)	7.5%	4-5	90°C	Toluene	97%	Present work

* Quantitative yield not provided, DBU: 1,8-Diazabicycloundec-7-ene, DBN: 1,5-Diazabicyclo [4.3.0]non-5-ene, PEG: Polyethylene glycol, DMF: Dimethyl formamide.

Table 4. Comparison of the literature and the present study for the preparation of compound 3.

Catalyst used	Catalyst loading	Time	Yield	Reference
2-Methyl-DABCO	2%	1.5/3	-*	[5]
DABCO	13%	2/3	65-78%	[29]
TBD	0.1-50%	1.0/4	High*	[30]
DABCO-based (CAT)	2%	1.5	78-80%	Present work

* Isolated yield not provided, DABCO: 1,4-Diazabicyclooctane, 2-Methyl-DABCO: 2-Methyl-1,4-diazabicyclooctane; TBD: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

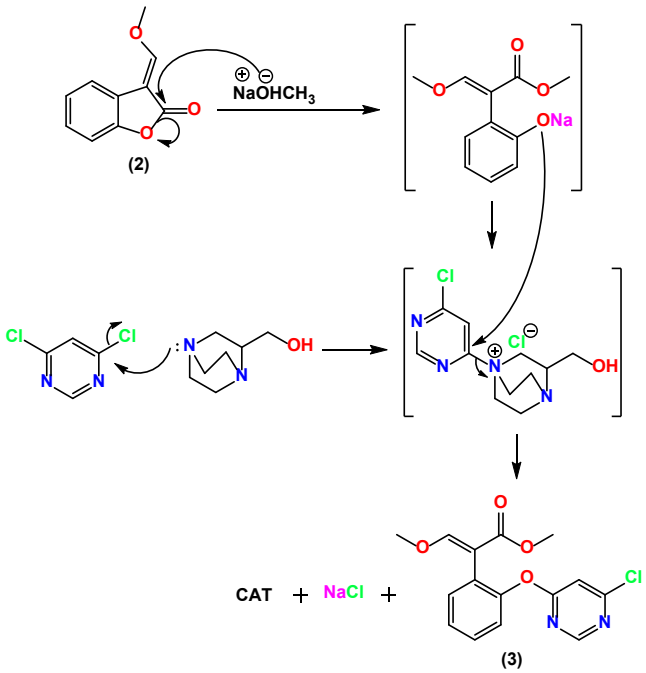


Figure 2. Proposed mechanism for the synthesis of compound 3.

Figure 3 illustrates the synthesis of azoxystrobin by CAT. The procedure was initiated by the reaction of 2-cyanophenol and K_2CO_3 in toluene, resulting in the formation of the potassium salt of 2-cyanophenol, which serves as a potent nucleophilic intermediate. Subsequently, this intermediate reacts with compound 3 mediated by CAT, resulting in the production of the target compound [23].

To evaluate the effectiveness of the developed catalytic system, the preparation of compounds 4 and 3 was compared with methods reported previously in the literature. The comparison considers key reaction parameters, including catalyst type and loading, reaction time, temperature, solvent, and product yield. As summarized in Tables 3 and 4, various catalytic systems reported in the literature exhibit different efficiencies under various reaction conditions. The results obtained in the present study demonstrate that the DABCO-based catalyst provides comparable or improved performance in terms of reaction time and yield, highlighting the efficiency and practicality of the proposed methodology relative to existing approaches.

4. Conclusions

In this study, we explored a new catalyst (CAT) that we used in both step for preparation of azoxystrobin. We were satisfied to find that this innovative catalyst gives impressive results, achieving around 97% yield for azoxystrobin. When we tested the same catalyst for its performance to synthesize an intermediate compound 3, it showed a yield of approximately 80%, which was significantly better than the traditional DABCO catalyst. In this study, the recommended 3 and 7.5% by mole found gives the optimum results. One of the distinguishing features of this process is its ability to facilitate tailor-made nucleophilic substitution. We believe that these results arise from the formation of a highly reactive quaternary ammonium intermediate. The route offers several practical benefits: it keeps costs down, is easy to carry out on-scale, and has a comparatively low environmental impact. These qualities make it an industry-friendly option for large-scale manufacturing. In general, this catalytic strategy not only streamlines the preparation of azoxystrobin, but also strengthens a range of other nucleophilic aromatic substitution reactions that have traditionally depended on established catalytic systems.

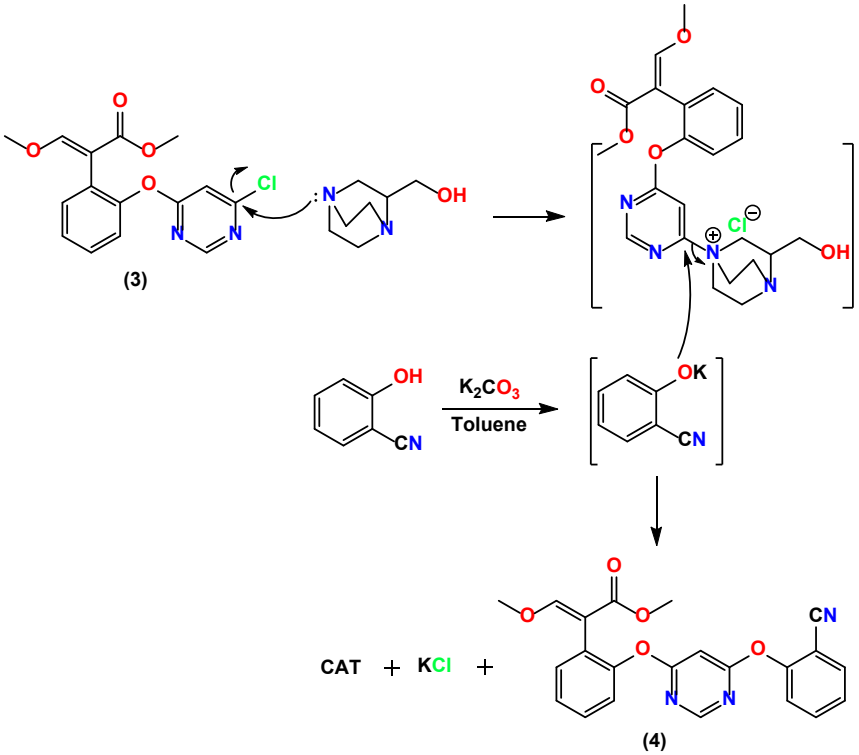


Figure 3. Proposed mechanism for the synthesis of compound 4.

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Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Nilesh Dattatraya Dhande, Hemant Prabhakar Narkhede; Methodology: Nilesh Dattatraya Dhande, Uday Vasudev Baviskar; Validation: Nilesh Dattatraya Dhande, Tushar Tulsidas Pansare; Formal Analysis: Nilesh Dattatraya Dhande, Hemant Prabhakar Narkhede; Investigation: Nilesh Dattatraya Dhande; Data Curation: Nilesh Dattatraya Dhande, Tushar Tulsidas Pansare; Writing - Original Draft: Nilesh Dattatraya Dhande, Tushar Tulsidas Pansare; Writing - Review and Editing: Hemant Prabhakar Narkhede; Administration: Hemant Prabhakar Narkhede.

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