# Synthesis and Characterization of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1--yl)ethan-1-one

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A simple and efficient method to prepare 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one *via* nucleophilic substitution of 2-chloro-1-(1-chlorocyclopropyl)ethanone and 1,2,4-triazole is described. The title compound is the key intermediate required for the synthesis of prothioconazole, a promising agricultural fungicide. By exploring changes in the reaction time, temperature, ratio of starting reagents, acid binding agent, and the nature of phase transfer catalyst, the reaction conditions could be optimized to afford the desired N-alkylated material in near-quantitative yield. The ultimate yield of the product after recrystallization was 93%, with a purity of 99% based on its characterization by Gas Chromatography-Mass Spectrometer (GC-MS), Fourier Transform infrared spectroscopy (IR), Proton Magnetic Resonance ($^1$H NMR), and Carbon-13 Nuclear Magnetic Resonance ($^{13}$C NMR). The synthetic process is suitable for industrial application, with the advantages of high yield and facile preparation under mild operating conditions.

**Keywords:** prothioconazole; 1,2,4-triazole; N- alkylation reaction.

## INTRODUCTION

Prothioconazole (CAS registration number is 178928-70-6) is a synthetic broad spectrum systemic fungicide in the triazolinthione class of compounds developed by Bayer AG[1–3]. Its fungicidal properties have been employed for curative, preventative, and eradicative means, principally in the management of fungal diseases of cereal and bean crops[4–7]. Most fungal diseases of wheat, including powdery mildew, eyespot, Fusarium wilt, early leaf spot, phoma leaf spot, rust, *Sclerotinia Sclerotiorum*, net blotch, and moire disease, are well controlled by prothioconazole formulations[8–10]. Among triazole fungicides, prothioconazole is noted for its increased spectrum of mycocidal activity and significantly greater efficacy in disease prevention and cure. Its good biological toxicity and ecotoxicity profiles indicate its relative safety for humans, plants, and the environment.

Four synthetic routes to prothioconazole have been described. A common approach utilizes 1-(1-chlorocyclopropyl)ethanone, 1,2,4-triazole, and 2-chlorobenzyl chloride as starting reagents (Fig. 1). In the initial step of this route, 1-(1-chlorocyclopropyl)ethanone and 1,2,4-triazole afford the key intermediate 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one by nucleophilic substitution reaction. However, the reaction fails to proceed to completion as 1,2,4-triazole has low solubility in organic solvents and, upon workup, the desired product is obtained in low yield and purity[11]. As 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one is a key reagent in the synthesis of prothioconazole, its preparation in a facile and environmentally friendly process is desirable.

This paper describes the investigation and optimization of conditions for the synthesis of 1-(1-chlorocyclopropyl)--2-(1,2,4-triazol-1-yl)ethan-1-one based on reported literature. Under the action of phase transfer catalyst(PTC), 2-chloro-1-(1-chlorocyclopropyl)ethanone and 1,2,4-triazole taken as the reactants THF and water as the mixed solvent, afford it by N-alkylation reaction. Using the characteristics of 1-(1-chlorocyclopropyl)-2-(1,2,4-
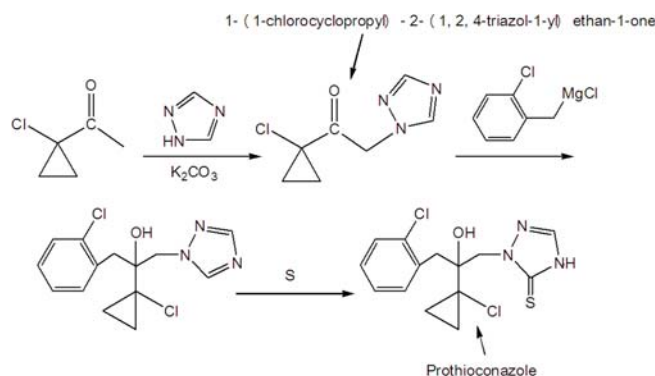


**Figure 1.** Synthetic route to prothioconazole

-triazol-1-yl)ethan-1-one and its nitrate, we selected the appropriate salt-forming conditions and the separation conditions to get high purity of 1-(1-chlorocyclopropyl)-2--(1,2,4-triazol-1-yl)ethan-1-one from its crude product. The optimized method is high yielding, has simple workup, and avoids chromatographic purification, making it better suited for industrial production.

## EXPERIMENTAL

2-chloro-1-(1-chlorocyclopropyl)ethanone (purity 80%) and 1,2,4-triazole (purity 99%) were obtained from Hubei Kang Baotai Fine Chemical Co., Ltd. Ultrapure water was used and other raw reagents used in the experiment were analytically or chemically pure.

Melting points were determined on a WRS-1B digital melting point apparatus, and the uncorrected values were used. Fourier transform infrared (FT-IR) spectra were taken in KBr on a Shimadzu 8400S spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded at 400MHz and 100 MHz, respectively, on a BRUKER AVANCE III HD 400 MHz NMR spectrometer. CDCl$_3$ was used as the solvent with TMS as the internal standard. The chemical shift values are reported in ppm($\delta$). Mass spectra were recorded on a GC-MS-2010-plus spectrometer (Shimadzu Corporation) and the fragmentations were

obtained by electronic impact (EI). The data are given as mass-to-charge ratios (m/z), and nominal masses were used for the calculation of molecular weights of the synthesized products.

## Synthesis of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl) ethan-1-one (Figure 2)

1,2,4-triazole (3.312 g, 0.048 mol), $K_2CO_3$ (7.176 g, 0.052 mol), and PEG-1000 (2 g, 5%, $2 \times 10^{-3}$ mol) were combined in 20 mL of water under stirring at room temperature. The mixture was heated for 1 h at 65°C. Maintaining a constant temperature, a solution of 2-chloro-1-(1-chlorocyclopropyl)ethanone (7.65 g, 0.04 mol) in 20 ml of THF was added drop-wise. After the addition, the reaction was stirred for 5 h before cooling to room temperature. The aqueous layer was separated and the product was extracted with THF. The combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one (98%) as a dark brown oil. The purity of the crude product was determined to be 73% by GC-MS.
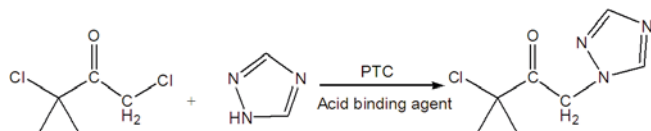


**Figure 2.** Synthesis of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol--1-yl)ethan-1-one

## Purification of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol--1-yl)ethan-1-one (Figure 3)

Concentrated nitric acid (7 g, 65%, 0.07 mol) was slowly added to a solution of the crude product in 100ml of carbon tetrachloride ($CCl_4$) at 30°C. After stirring for one hour, a white precipitate formed. The solution was cooled to 15°C and the precipitate filtered.

The salt was dissolved in 80ml ethyl acetate and heated to 30°C. The solution was neutralized with the addition of 30% aqueous sodium hydroxide and then stirred for 0.5h at this temperature. After cooling to room temperature, the aqueous layer was separated and the product was extracted with ethyl acetate. The combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 6.88 g of white crystals. After recrystallization, the desired product was returned in 93% yield with 99% purity, as determined by GC-MS.

## RESULTS AND DISCUSSION

### The selection of solvents

Initial experiments used water, acetone, THF, or ethyl acetate as the solvent, but the two reagents 2-chloro--1-(1-chlorocyclopropyl)ethanone and 1,2,4-triazole do not readily dissolve in the same conditions, and so, the reaction was typically low yielding. Because of its wide liquid range, THF is a frequently used moderately polar aprotic solvent. Its moderate polarity engenders a stabilizing effect advantageous for the $S_N^2$ reaction and also facilitates the participation of an ionic base in the reaction[12]. Finally, the use of a mixed aqueous and organic solvent can increase the yield of a phase-transfer catalytic reaction and reduce post-treatment steps.

### The selection of acid binding agent

Amines participate in nucleophilic substitution reactions with alkyl halides to yield more highly substituted amines. The hydrogen halide generated in the reaction forms ammonium salt byproducts, which can be reaction limiting. Acid binding agents such as an excess of amine, sodium carbonate, or pyridine drive the reaction equilibrium toward the desired alkylamine by adhering to the displaced hydrogen halide.

We explored the effects of different acid binding agents on the yield in the nucleophilic substitution reaction depicted in Figure 2. Maintaining constant conditions of temperature, reaction time, and reagent ratios, five bases were evaluated as acid binding agents. The results are shown in Table 1. As is apparent from the data displayed in Table 1, yields were maximized when using $K_2CO_3$ as the acid binding agent, returning 98.3% of the desired alkylamine. Reactions with the stronger bases NaOH and KOH yielded other undesirable byproducts, while the weaker bases triethylamine and $Na_2CO_3$ failed to drive the reaction to completion.

### The selection of phase-transfer catalyst

Typically, reactions performed in a homogeneous phase allow for ready interaction of the reactants. However, for reactions that necessitate heterogeneous phases, the rate can be considerably limited by the reduced contact between reagents in heterogeneous phases. In some instances, a phase-transfer catalyst (PTC) can be employed to improve the reaction performance. Recently, considerable attention has been devoted to heterogeneous catalysis and the wide utility of PTCs[13].

Commonly used PTCs include quaternary ammonium salts, polyethylene glycols (PEGs), and crown ethers. Crown ethers have excellent catalytic abilities as PTCs, achieving near-quantitative conversion to products. However, from a practical standpoint, their high cost and toxicity were limitations for their application to our purposes. Consequently, we evaluated several PEGs and quaternary ammonium salts as PTCs for the N-alkylation of 1,2,4-triazole[14–15]. The relative catalytic efficiency of each is displayed in Table 2, revealing the highest conversion rate for PEG-1000. The quaternary ammonium salts tetra-*n*-butylammonium bromide (TBAB) and cetyl trimethylammonium bromide (CTAB) had the least effective phase-transfer abilities. Accordingly, PEG-1000 represented a suitable phase-transfer catalyst for our synthesis of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl) ethan-1-one.
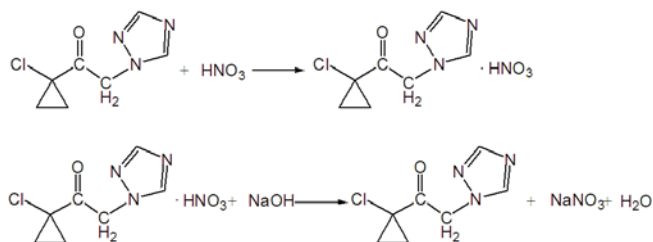
**Table 1.** Yield of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one using different acid binding agents

| Acid binding agent | KOH | NaOH | $K_2CO_3$ | Triethylamine | $Na_2CO_3$ |
|---|---|---|---|---|---|
| Yield [%] | 85.5 | 90.7 | 98.3 | 94.3 | 80.6 |

**Table 2.** Yield of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl) ethan-1-one using different phase transfer catalysts for N-alkylation of 1,2,4-triazole

| No. | PTC | Yield [%] |
|---|---|---|
| 1 | PEG-400 | 93.50 |
| 2 | PEG-600 | 91.01 |
| 3 | PEG-1000 | 98.36 |
| 4 | $C_{16}H_{36}BrN$ (TBAB) | 93.57 |
| 5 | $C_{19}H_{42}BrN$ (CTAB) | 91.83 |

PTC = phase transfer catalyst; PGE = polyethylene glycol; TBAB = tetra-n-butylammonium bromide; CTAB = cetyl triethylammonium bromide

**Figure 3.** Purification of 1-(1-chlorocyclopropyl)-2-(1,2,4--triazol-1-yl)ethan-1-one via chemical purification
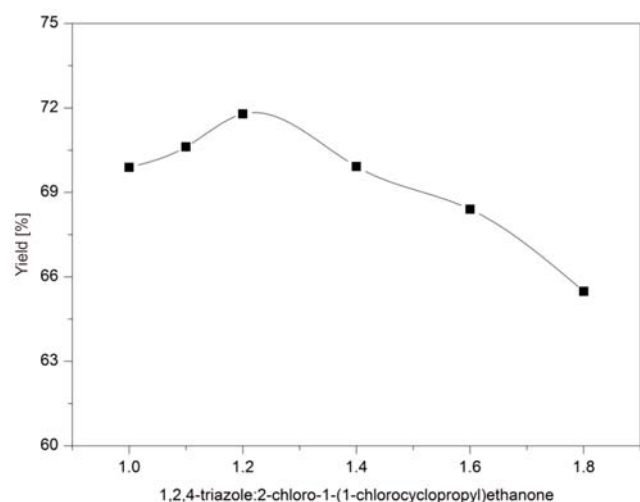
**Figure 4.** Effect of mole ratio on yield

### Effect of molar ratio on yield of the reaction

We explored the effect of increasing the molar ratio of the amine to alkyl halide, while maintaining stable reaction conditions of 5 h of reaction time at 50°C. Equimolar quantities of 2-chloro-1-(1-chlorocyclopropyl)ethanone (7.65 g, 0.04 mol) and $K_2CO_3$ (5.52 g, 0.04 mol), and a catalyst loading of 5% PEG-1000 (2 g, $2 \times 10^{-3}$ mol), were used in each run, as the ratio of 1,2,4-triazole to 2-chloro-1-(1-chlorocyclopropyl)ethanone was increased. Figure 4 shows the influence of increasing the ratio on product yield. Peak yield (71.8%) was achieved when the ratio of 1,2,4-triazole to 2-chloro-1-(1-chlorocyclopropyl) ethanone was 1.2:1.0.

### Effect of molar equivalents of $K_2CO_3$ on yield

Similarly, the effect of increasing the molar ratio of the acid binding agent $K_2CO_3$ to 2-chloro-1-(1-chlorocyclopropyl)ethanone on the yield was studied, under otherwise similar conditions. Figure 5 shows the yields obtained when equimolar 2-chloro-1-(1-chlorocyclopropyl)ethanone (7.65 g, 0.04 mol) and 1,2,4-triazole (2.76 g, 0.04 mol), with 5% PEG-1000 (2 g, $2 \times 10^{-3}$ mol),
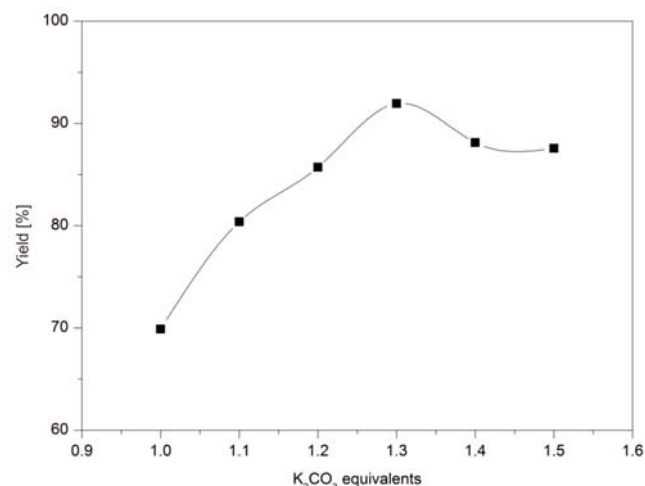
**Figure 5.** Effect of molar equivalents of $K_2CO_3$ on yield

were combined, with increasing quantities of $K_2CO_3$ for 5 h at 50°C.

As revealed in Figure 5, the relative amount of $K_2CO_3$ had a marked influence on product yield. Initially, an increase in the ratio of $K_2CO_3$ led to a proportional increase in the yield of product. Above 1.3 molar equivalents of $K_2CO_3$ with respect to 2-chloro-1-(1-chlorocyclopropyl) ethanone, the reactions returned increasing amounts of byproducts, at the expense of the desired material; thus, the yield declined. We postulate that the excess alkali contributed to these unwanted products. The product yield was maximized at 92.0%, when the ratio of $K_2CO_3$ to 2-chloro-1-(1-chlorocyclopropyl)ethanone was 1.3:1.0.

### Effect of reaction temperature on yield

With a consistent 1:1:1 molar ratio of 2-chloro-1-(1--chlorocyclopropyl)ethanone to 1,2,4-triazole and $K_2CO_3$, a reaction time of 5 h, and a PTC loading of 5% PEG-1000, the effect of reaction temperature on the yield was explored. The results are shown in Figure 6. From 30–65°C, an increase in the reaction temperature delivered increasing yield of product, peaking at 75.3% at 65°C.
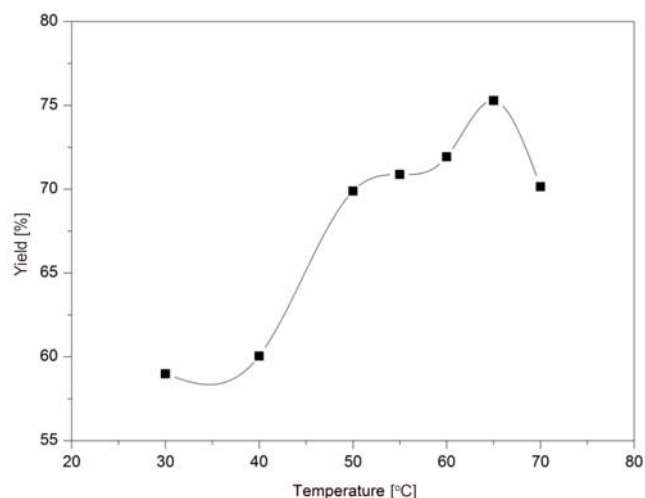
**Figure 6.** Effect of reaction temperature on yield

Above 65°C, the reaction of byproducts became more prevalent, and the yield of the desired target decreased.
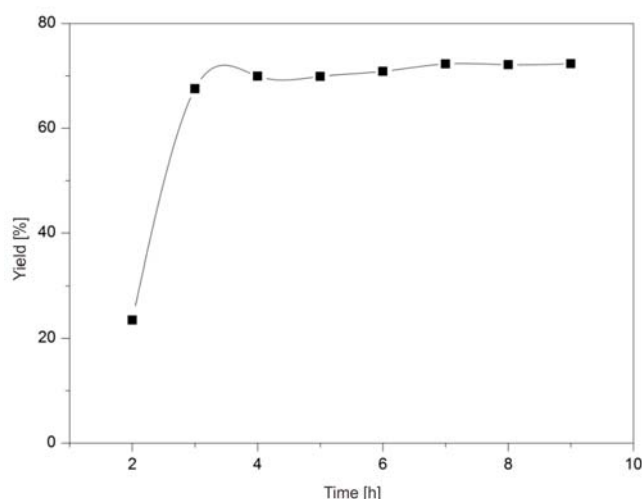
**Figure 7.** Effect of reaction time on yield

### Effect of reaction time on yield

Finally, the effect of reaction time on the yield of the product was studied, with the results shown in Figure 7. As previously, a constant 1:1:1 molar ratio of 2-chloro-1-(1-chlorocyclopropyl)ethanone to 1,2,4-triazole and K₂CO₃ with 5% PEG 1000 was used for all runs, which were performed at 50℃. With increasing reaction time, product yield also increased. A significant effect was observed with an increase from two to three hours, with gradually higher returns thereafter. Beyond seven hours, at 72.3% yield, no further improvement was observed.

### Orthogonal experiment

Ultimately, the optimal reaction conditions for the preparation of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-

-1-yl)ethan-1-one were determined by orthogonal experimental design. The yield was used as the test index, and a set of orthogonal tests with four factors and four levels was designed (Table 3). Analysis of the orthogonal experiment indicates the optimum combination of reaction conditions entail a molar ratio of 1.0:1.2:1.3 for 2-chloro-1-(1-chlorocyclopropyl)ethanone to 1,2,4-triazole to K₂CO₃, a reaction time of 5 h, and a temperature of 65℃.Under these conditions, a crude yield of 98.4% could be achieved.

### The reproducibility of the experiment

The reaction conditions were optimized by single factor experiments and orthogonal experiment design. Under the optimum reaction conditions, we can verify the repeat-preparation possibility of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one by 6 times repeated experiments (Table 4). It shows that the best optimization outcome has a good repeatability after using in the test experiment. The repetition of the experiment is good and warp is small. Under these conditions, the highest yield was up to 98.75%, and the mean yield was 98.28%.

### The principle of removing impurities

In the process of the exploration, we found that 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1--one and the concentrated nitric acid have an excellent salt-forming performance, and the salt is insoluble in certain organic solvents but can be re-dissociated by the base. According to the characteristics of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one and its nitrate, we could effectively purify the crude product of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one

**Table 3.** Results and analysis of orthogonal test for experimental conditions

| No. | Reaction temperature [°C] | Ratio of 1,2,4-triazole to 2-chloro-1-(1-chloro-cyclopropyl) ethanone | Ratio of K₂CO₃ to 2-chloro-1-(1-chloro-cyclopropyl) ethanone | Reaction time [h] | Yield [%] |
|---|---|---|---|---|---|
| 1 | 50 | 1.1:1.0 | 1.1:1.0 | 5 | 65.70 |
| 2 | 50 | 1.2:1.0 | 1.2:1.0 | 6 | 82.14 |
| 3 | 50 | 1.3:1.0 | 1.3:1.0 | 7 | 83.26 |
| 4 | 50 | 1.4:1.0 | 1.4:1.0 | 8 | 84.90 |
| 5 | 55 | 1.1:1.0 | 1.2:1.0 | 7 | 86.62 |
| 6 | 55 | 1.2:1.0 | 1.3:1.0 | 8 | 82.21 |
| 7 | 55 | 1.3:1.0 | 1.4:1.0 | 5 | 95.38 |
| 8 | 55 | 1.4:1.0 | 1.1:1.0 | 6 | 78.68 |
| 9 | 60 | 1.1:1.0 | 1.3:1.0 | 8 | 84.65 |
| 10 | 60 | 1.2:1.0 | 1.4:1.0 | 7 | 94.23 |
| 11 | 60 | 1.3:1.0 | 1.1:1.0 | 6 | 57.46 |
| 12 | 60 | 1.4:1.0 | 1.2:1.0 | 5 | 77.92 |
| 13 | 65 | 1.1:1.0 | 1.4:1.0 | 6 | 93.41 |
| 14 | 65 | 1.2:1.0 | 1.3:1.0 | 5 | 98.36 |
| 15 | 65 | 1.3:1.0 | 1.2:1.0 | 8 | 78.76 |
| 16 | 65 | 1.4:1.0 | 1.1:1.0 | 7 | 83.68 |
| $K_1$ | 316 | 330.38 | 285.52 | 337.39 | |
| $K_2$ | 342.89 | 356.97 | 325.44 | 311.69 | |
| $K_3$ | 314.26 | 314.86 | 348.51 | 347.79 | |
| $K_4$ | 354.24 | 325.18 | 367.92 | 330.52 | |
| $k_1$ | 79.00 | 82.60 | 71.38 | 84.35 | |
| $k_2$ | 85.72 | 89.24 | 81.36 | 77.92 | |
| $k_3$ | 78.57 | 78.72 | 87.13 | 86.95 | |
| $k_4$ | 88.56 | 81.30 | 91.98 | 82.63 | |
| R | 9.56 | 7.95 | 20.60 | 4.71 | |

**Table 4.** Repeat experiment results

| No. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Yield [%] | 98.45 | 98.17 | 98.12 | 98.34 | 97.84 | 98.75 |

and the desired product had high recovery rate and product purity under the appropriate salt-forming and dissociation conditions.

Since 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)--ethan-1-one are easily dissolved in water and the nitrate formed by it and $HNO_3$ are unstable in hot water, the nitric acid used for salt formation should be at a sufficiently high concentration so as to increase the yield of the salt formation reaction. Selecting solvent should meet two necessary conditions: the solvent has good solubility to 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1--one to ensure that the form of the nitrate in solution and the solvent does not dissolve the nitrate so as to ensure that the nitrate is not lost during separation and dissociation. Therefore, the selected salt-forming solvent was $CCl_4$, and the dissociation solvent was $CCl_4$ or ethyl acetate in the experiment. The concentration of nitric acid was 65–68%.

### Structural characterization of the target compound

We obtained the target by chemical purification, and its composition and structure were characterized by GC--MS, FT-IR, ^{1}H NMR, ^{13}C NMR. The detailed analysis was carried out, and the corresponding coupling constant (*J value*) was given. The structure and the atomic number of the target compound are shown in Figure 8. After recrystallization of our target compound, its composition and structure were characterized by GC-MS, FT-IR, ^{1}H NMR, and ^{13}C NMR. Thorough analysis including the identification of corresponding coupling constants (*J value*) was performed. The structure and atomic numbering for the target compound are shown in Figure 8.
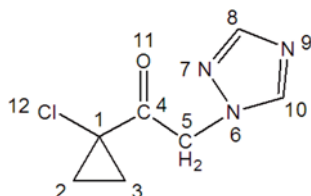


**Figure 8.** Molecular structure and atomic numbering of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one
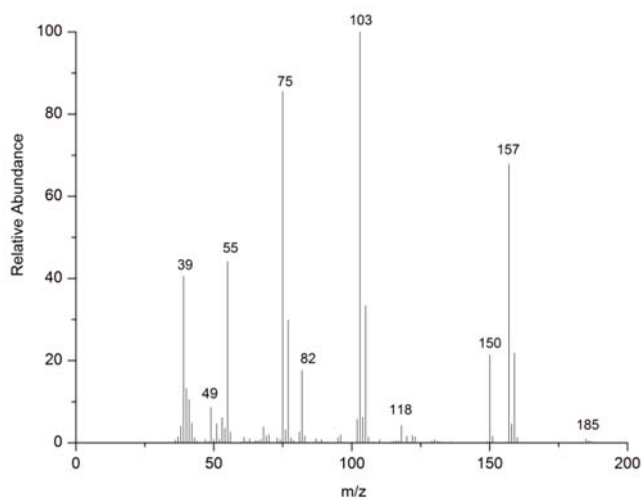


**Figure 9.** Mass spectrum of 1-(1-chlorocyclopropyl)-2-(1,2,4--triazol-1-yl)ethan-1-one

### Mass spectral analysis

In the mass spectra of the target product (Fig. 9), the molecular ion peak of the target molecule is very small, meanwhile, there are absorption peaks of triazole ring fragments and the fragments of triazole ring off $N_2$. The structure of the target compound containing Cl atoms, accordingly the characteristic peak of Chloride Isotopes exists in the mass spectrum, which is due to the natural abundance ratio of [37]Cl and [35]Cl in nature is approximately 1:3. This feature provides a very useful basis for the qualitative analysis and debris of the fragments[16]. The mass spectrum of the target product (Fig. 9) affords a very small molecular ion peak at m/z = 185. More substantial peaks indicate fragmentation of the triazole ring with loss of $N_2$ (m/z = 157) and the base peak at m/z = 103 corresponds to loss of the triazole ring and α-methylene. Another substantial peak at m/z = 75 represents the chlorocyclopropyl fragment. The presence of a chloride atom in the target compound is indicated by the characteristic 1:3 ratio of mass spectral fragments containing this element, determined by the natural abundance of chloride isotopes [37]Cl and [35]Cl. This feature provides a useful basis for the qualitative identification of fragments[16]. We propose that the putative fragmentation pathways displayed in Figure 10 account for the main ions (m/z = 185, 157, 150, 118, 103, 82, 75, 68, 55, 39) in the mass spectrum of the target compound.

### FT-IR analysis

Characteristic absorptions of the sample cover the entire range from 4000–400 cm$^{-1}$ (Fig. 11). The bands at 3133.2 cm$^{-1}$, 3099.8 cm$^{-1}$, 2972.2 cm$^{-1}$, and 2946.8 cm$^{-1}$ represent characteristic absorptions for C-H stretching vibrations in the triazole ring and saturated C-H stretching vibrations. A strong absorption peak at 1719.5 cm$^{-1}$ indicates the stretching vibration of the C=O group, while another strong absorption at 1508.8 cm$^{-1}$ suggests the C-N stretching vibration. A peak at 1460 cm$^{-1}$ could be attributed to the $CH_2$ scissoring vibration. Stretching vibrations of the C-C in cyclopropyl could be indicated by the strong absorption peak at 1297.5 cm$^{-1}$. Absorption bands of medium intensity from 1210–1100 cm$^{-1}$ appeared to be due to the in-plane bending vibration of C-H in the triazole ring, and a medium absorption peak located at 1072.4 cm$^{-1}$ was due to the stretching vibration of the carbonyl carbon and the alkyl carbon. Absorptions at 894.2 cm$^{-1}$ and 874.7 cm$^{-1}$ and a band at 690–670 cm$^{-1}$ could be due to C-H bending vibrations and out-of-plane bending vibration of the triazole ring, respectively. An absorption peak at 453.3 cm$^{-1}$ may be accounted for by the C-Cl stretching vibration.

### The assignments of ^{1}H and ^{13}C in NMR spectra

In the ^{1}H NMR spectrum of 1-(1-chlorocyclopropyl)--2-(1,2,4-triazol-1-yl)ethan-1-one (Fig. 12), two signals without coupling located at 8.148 ppm (1H, s) and 7.994 ppm (1H, s) were assigned to H-8 and H-10, respectively. The aromatic hydrogens (especially α-H) experience a strong deshielding effect from the heteroaromatic triazole group[17]. A resonance at 5.612 ppm (2H, s) is indicative of the methylene protons at H-5, which are influenced by the electron-withdrawing effect of the
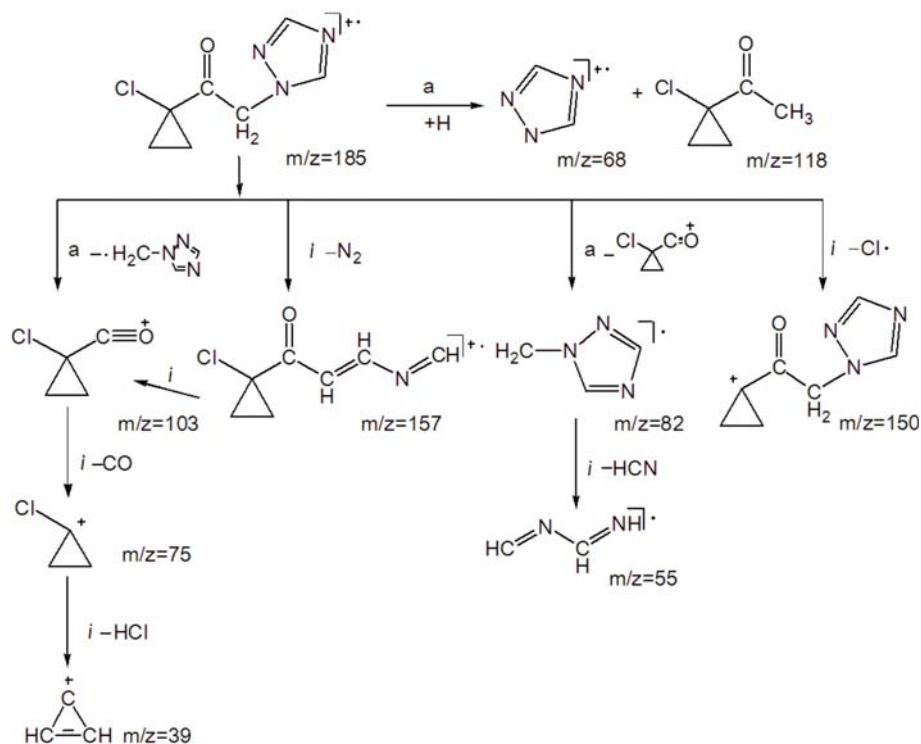
**Figure 10.** Proposed fragmentation pathways of 1-(1-chloro-cyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one
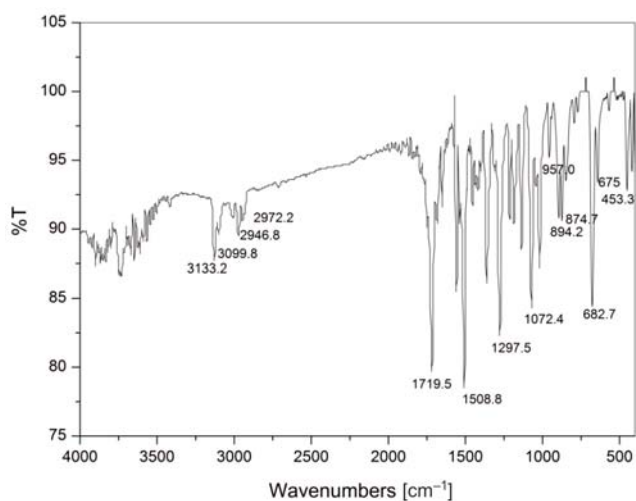


**Figure 11.** IR spectrum of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one

triazole and carbonyl groups, shifting the resonance downfield. The cyclopropyl protons display two multiplet resonances, each integrating for two protons, at 1.771–1.805 ppm (2H, m, J = 8.39 Hz) and 1.502–1.537 ppm (2H, m, J = 8.39 Hz) for H-2 and H-3, respectively. Each of the resonances at H-2 and H-3 appears as four peaks, presumably indicating coupling interactions with the germinal and vicinal protons with coupling constants of comparable magnitude. The $^{13}$C NMR spectrum of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one (Fig. 13) reveals three signals at 150.2 ppm, 144.6 ppm, and 56.8 ppm, which were assigned to C-8, C-10, and C-5, respectively. The signal located at 23.7 ppm indicates the cyclopropyl methylene carbons, C-2 and C-3. The α-haloketone carbonyl C-4 is evident at 198.6 ppm, where the electron-donating effect of the cyclopropyl group shifts the signal upfield. The signal at 44.7 ppm was assigned to the quaternary carbon, C-1. These as-
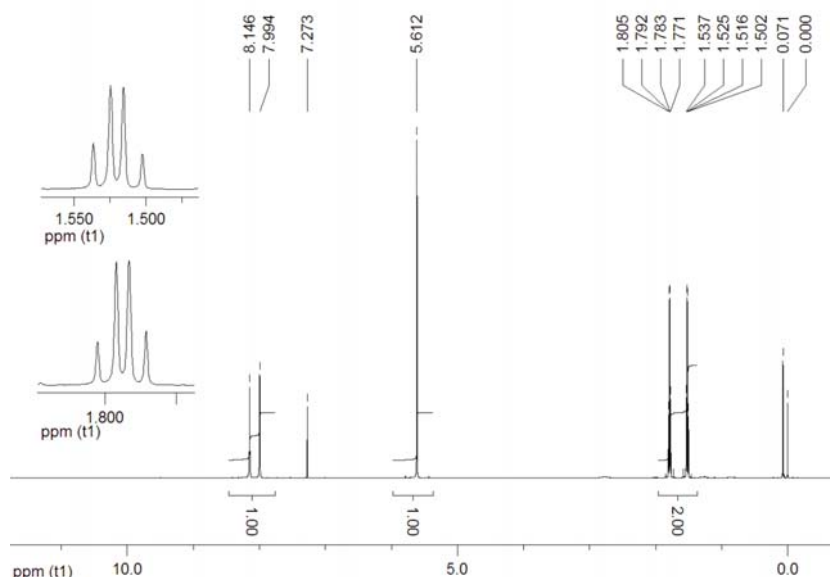


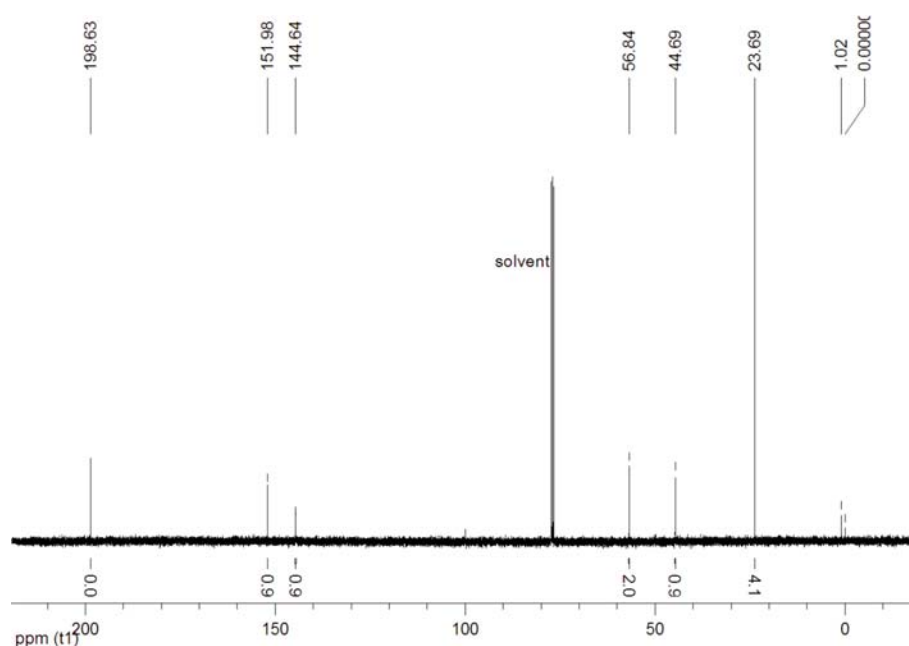**Figure 12.** $^1$H NMR of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one

**Figure 13.** $^{13}$C NMR of 1-(1-chlorocyclopropyl)-2-(1,2,4-triazol-1-yl)ethan-1-one

signments agree with the interpretation of the integral curve of each signal. The spectral findings were consistent with the data anticipated for the target material.

## CONCLUSION

In our study of synthetic approaches toward the 1,2,4-triazole fungicides represented by prothioconazole, one of the key intermediates, 1-(1-chlorocyclopropyl)--2-(1,2,4-triazol-1-yl)ethan-1-one, was obtained. Its composition and structure were characterized by GC-MS, FT-IR, $^1$H NMR, and $^{13}$C NMR, which agree with data expected for the material. The reaction conditions were optimized by single factor experiments and orthogonal experiment design to achieve near-quantitative yield of the desired target. Our method improves on previous syntheses in that it achieves exceptional yield, with simple workup, reducing loss of product. Impurities are readily removed through chemical purification, avoiding column chromatography, which makes the synthesis favorable for industrial production.

## ACKNOWLEDGEMENTS

## LITERATURE CITED

1. Gold, R.E., Bestman, H. & Haden, E. (2008). Patent No. 20110105320 A1. Washington, D.C.: U.S. Patent and Trademark Office.

2. Edwards, S.G. & Godley, N.P. (2010). Reduction of Fusarium head blight and deoxynivalenol in wheat with early fungicide applications of prothioconazole. *Food Addit. Contam.* 27(5), 629–635. DOI: 10.1080/19440040903515942.

3. Xavier, S.A., Canteri, M.G. & Barros, D. (2013). Sensitivity of Corynespora cassiicola from soybean to carbendazim and prothioconazole. *Trop. Plant Pathol.* 38(5), 431–435. DOI: 10.1590/S1982-56762013005000020.

4. Schisler, D.A. & Boehm, M.J. (2012). U.S. Patent No. 8,241,889. Washington, D.C.: U.S. Patent and Trademark Office.

5. Liu, M., Liu, H. & Li, P.R. (2003). Synthesis of 3-mercapto-4-oxopentyl acetate. *Appl. Chem. Ind.* 32(6), 53–54. DOI: 10.16581/j.cnki.issn1671-3206.2003.06.021.

6. Klaus, S., Wilhelm, B. & Stefan, D. (1990). U.S. Patent No. 4,913,727. Washington, D.C.: U.S. Patent and Trademark Office.

7. Linke, S.W., Mohrmann, K.H. & Reiser, W. (1991). U.S. Patent No. 4,992,565. Washington, D.C.: U.S. Patent and Trademark Office.

8. Schisler, D.A., Boehm, M.J. & Paul, P.A. (2015). Reduction of Fusarium head blight using prothioconazole and prothioconazole-tolerant variants of the Fusarium head blight antagonist Cryptococcus flavescens OH 182.9. *Biol. Control.* 86, 36–45. DOI: 10.1016/j.biocontrol.2015.04.002

9. Parker, J.E., Warrilow, A.G.S. & Cools, H.J. (2013). Prothioconazole and prothioconazole-desthio activities against Candida albicans sterol 14-α-demethylase. *Appl. Environ. Micro.* 79(5), 1639–1645. DOI: 10.1128/AEM.03246-12.

10. Haidukowski, M., Visconti, A. & Perrone, G. (2012). Effect of prothioconazole-based fungicides on Fusarium head blight, grain yield and deoxynivalenol accumulation in wheat under field conditions. *Phytopat. Medit.* 51(1), 236–246. DOI: 10.14601/Phytopathol Mediterr-9401.

11. Fu, Q., Shen, D. & Yuan, Q.L. (2005). Reviews on Synthetic Methods of Prothioconazole. *Henan Chem. Ind. 22(5)*, 8–10. DOI: 10.14173/j.cnki.hnhg.2005.05.003.

12. Loudon, G. M. (2002). *Organic Chemistry (4th ed.)*. New York, USA: Oxford University Press.

13. Halpern M.P. (2012). *Transfer Catalysis*. Wiley-VCH Verlag GmbH & Co. KGaA.

14. Sankarshana, T., Yadagiri, E. & Murthy, J.S.N. (2014). Phase Transfer Catalysis:Oxidation of 2-Methyl-1-butanol. *Chin. J. Chem. Eng.* 22(9), 1000–1004. DOI: 10.1016/j.cjche.2014.06.023.

15. El-Sayed, A.M., Allah, O.A.A. & El-Saghier, A.M.M. (2014). Synthesis and Reactions of Five-Membered Heterocycles Using Phase Transfer Catalyst (PTC) Techniques. *J. Chem.* 2014(25), 1000–1004. DOI: 10.1155/2014/163074.

16. Li, X., Wang, Y.W., Gu J.K., Zhong, D.F., Wang, L. & Chen, G. (2003). Fragmentation Behaviors of Triazolobenzodiazepines by Electrospray Ionization/Quadrupole Time-of-Flight Mass Spectrometry. *Anal. Biochem.* 31(9), 1105–1108. DOI: 10.3321/j.issn:0253-3820.2003.09.021.

17. Ning, Y.C. & Richard, R.E. (2005). *Structural Identification of Organic Compounds with Spectroscopic Techniques*. Wiley-VCH Verlag GmbH & Co. KGaA.