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An elementary study of the industrialized preparation of 1,1-difluoro acetone: Starting material of fluoropyrazole succinate dehydrogenase inhibitor

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ABSTRACT

In recent years, the development and increasing market presence of fungicides incorporating a fluoropyrazole ring, recognized as succinate dehydrogenase inhibitor fungicides, has gained momentum. The fluoropyrazole ring stands as the foundational nucleus of these fungicides, with its production cost being a pivotal concern for chemical industries. Significantly, the cost of 1,1-difluoro acetone largely influences this manufacturing cost. A cost-effective availability of 1,1-difluoro acetone could revolutionize the current methodologies for fluoropyrazole ring synthesis, primarily due to its enhanced safety and environmental sustainability. This study introduces an industrialized production methodology for 1,1-difluoro acetone, underlining its economic efficiency. Originating from ethyl acetoacetate, dibromide is synthesized in n-heptanol through the Oxone/KBr system. Following a fluorine-bromine exchange reaction with potassium fluoride, difluoride is obtained. Subsequent hydrolysis of the difluoride using 50% sulfuric acid leads to the formation of 1,1-difluoro acetone. Notably, while bromination and fluorination stages employ tubular reactors, hydrolysis, and decarboxylation are achieved in standard reactors. Optimal bromination conditions were identified as 2.2 equivalent bromination reagent, temperature>60°C, and atmospheric pressure. The fluorination conditions mirror those of bromination, with the fluorinating agent being 2.2 equivalent and a reaction temperature of 150°C. For hydrolysis and decarboxylation, 50% sulfuric acid concentration at 90°C was optimal, yielding a crude product with a 99.60% G.C. content and a 91.25% efficiency. The outlined production process of 1,1-difluoro acetone boasts remarkable cost efficiency and procedural simplicity, positioning it favorably for industrial applications. This innovative approach promises significant manufacturing cost reductions, endowing fungicides with a fluoropyrazole ring a competitive edge in the market. Such advancements are anticipated to foster market expansion, ultimately benefiting agricultural practitioners.

1. Introduction

Succinate dehydrogenase belongs to the cytochrome oxidase family and is found embedded in the inner membrane of mitochondria. This vital enzyme provides electrons for the aerobic and productive respiratory chain in eukaryotic mitochondria. As such, succinate dehydrogenase is a prime target for inhibition. Recent research, such as that by Wang et al. (2021), has highlighted succinate dehydrogenase inhibitors (SDHIs) as a significant tool in preventing disease by compromising the energy synthesis of pathogenic bacteria. Essentially, these inhibitors thwart the respiratory function of mitochondria, leading to the pathogen's eventual death due to its inability to generate energy in the usual manner. This mechanism is fundamental for

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disease prevention and treatment. Succinate dehydrogenase inhibitors play a pivotal role in the realm of fungicides. Furthermore, the synthesis of 1,1-difluoroacetone emerges as a potentially groundbreaking molecule in this domain, paving the way for novel advancements in both fungicide development and the broader scope of chemical synthesis. The following sections will delve into the typical applications of these inhibitors.

Pydiflumetofencan is used to treat Fusarium Head Blue (FHB), which leads to the decline of small grain yield and quality to avoid grain contamination by mycotoxins. This protection is achieved through the fungicide's ability to inhibit the development of FHB fungal spores in grains. It works by disrupting fungal cell membrane development; as a result, FHB spores cannot develop and grow, and germination and sporulation of FHB fungi are inhibited.

A new generation of succinate dehydrogenase inhibitor pidefromotifen is used to control one of the airborne diseases, gray mold, caused by gray mold, which can lead to crop yield loss (Li et al., 2022). Thiafluzolamide has high inhibitory activity against Rhizoctonia (Zhao et al., 2022). Succinate dehydrogenase inhibitor fungicide protects plants. It prevents Alternaria Rot (A. R.) by inhibiting cell respiration. This fungal disease causes leaf patches, black stem discoloration, and fruit rot in California citrus trees. Active spores in the air may impair fruit quality and production and kill affected plants.

Propiconazole inhibits succinate dehydrogenase, inhibiting the fungus's metabolic enzyme pathway for cell respiration. The fungus and its cells get their energy from this enzyme, which is needed for spore germination and disease development in sensitive plants. Succinate dehydrogenase inhibitor fungicide helps prevent and treat citrus mycosis in California. This fungicide prevents Alternaria rot by inhibiting cell respiration. To safeguard California's citrus trees, soil and foliage treatments should be used more (Camiletti et al., 2022). Succinate dehydrogenase inhibitor fungicides can be effectively used for infection of Alternaria Solani, Alternaria Dendriformis, and Alternaria Tenuis (Budde-Rodriguez et al., 2022).

Among multitudinous succinate dehydrogenase inhibitor fungicides, the lipophilicity, PKa, conformation, and bioavailability of fluoro pyrazole compounds are at an appropriate level due to the unique electronegativity, electronic effect and steric hindrance effect of fluorine atom (Chen et al., 2022), and multi-directional transformation of substituents on pyrazole ring is a superimposed factor, which shows the characteristics of high efficiency, low toxicity, structural diversity, and extensive biological activity, and plays a more and more critical role, leads to broad prospects of industrialization research in-depth (Ghasempour et al., 2021). Fluoropyrazole succinate dehydrogenase inhibitor fungicides have novel action mechanisms, long-lasting efficacy, significant yield increase, and strong market performance in recent years, which are new fields competed by major pesticide companies (Aufiero and Gilmour, 2018). The exemplary compound structures are shown in Fig. 1.

It can be seen from Fig. 1 that the molecular structures of fluoro pyrazole succinate dehydrogenase inhibitor fungicides contain a similar fluorinated pyrazole ring, and the industrialized preparation of the fluorinated pyrazole ring is inseparable from a fluorinated compound named 1,1-difluoro acetone. 1,1-Difluoro acetone is a $C_3H_2F_2O$ chemical molecule (Surya et al., 2010). It is colorless, soluble in organic solvents, and hard to remove from water. 1,1-difluoro acetone is used to synthesize medicines and hydrogen peroxide. Fluorinated chemicals such as 1H-pyrazoles, 3-amino-pyrrolidines, and alexipharmic derivatives are made from it. 1,1-Difluoro acetone is the base of numerous vital fungicides, including fluopyrazole succinate, 2-fluorobenzcarboxamide succinic anhydride, and 2-fluorobutyrate succinic anhydride (Su et al., 2021). Methyl iodide combines with acetone to generate CH_3COCH_2F, which is oxidized to 1,1-difluoro acetone by oxygen or air (Golovanov et al., 2021). 1,1-difluoro acetone is used to make organofluorine polymers, nanoparticles, and electronic devices. It purifies steroids, gels, surfactants, and polystyrene.

Thanks to its reactivity, 1,1-difluoro acetone has several industrial uses. Destructive distillation dechlorinates halogenated hydrocarbons. Reacting with halogens yields fluorinated hydrocarbons. 1,1-difluoro acetone is employed in laboratory and industrial syntheses in many sectors due to its flexibility and reactivity. Its primary usage is in drug production. It synthesizes numerous vital fungicides, including fluopyrazole succinate dehydrogenase inhibitor, 2-fluorobenzcarboxamide succinic anhydride, 2-fluorobutyrate succinic anhydride, 2-fluoro benzamides, and others. 1,1-difluoro acetone has several commercial and laboratory uses. Its varied physical and chemical features allow it to synthesize organic molecules, medicines, and other substances utilized in numerous sectors, as shown in Fig. 2.

With sustained sales growth of fluoropyrazole succinate dehydrogenase inhibitor fungicides, the market demand for 1,1-difluoro acetone is also increasing. In addition, 1,1-difluoro acetone also has a certain consumption in pyrazole anti-inflammatory drugs, mTORC1 targeted drugs, Chiral-1,1-difluoro-2-propanol, modulators of interleukin-17 or ion channels, inhibitors of hematopoietic prostaglandin D synthase, NF-kB-inducing kinase, and other fields. Therefore, studying the industrial preparation method of 1,1-difluoro acetone is of great significance. 1,1-difluoro acetone (1,1-DFA) is an important intermediate for synthesizing drugs, agrochemicals, and other chemicals. It is widely used in the Synthesis of pesticides, such as phenothiazine, trifloxystrobin, and isooxazoline derivatives, and also used as an intermediate or building block in the Synthesis of pharmaceuticals and agrochemicals. As such, 1,1-DFA has been intensively studied in academic and industrial research.

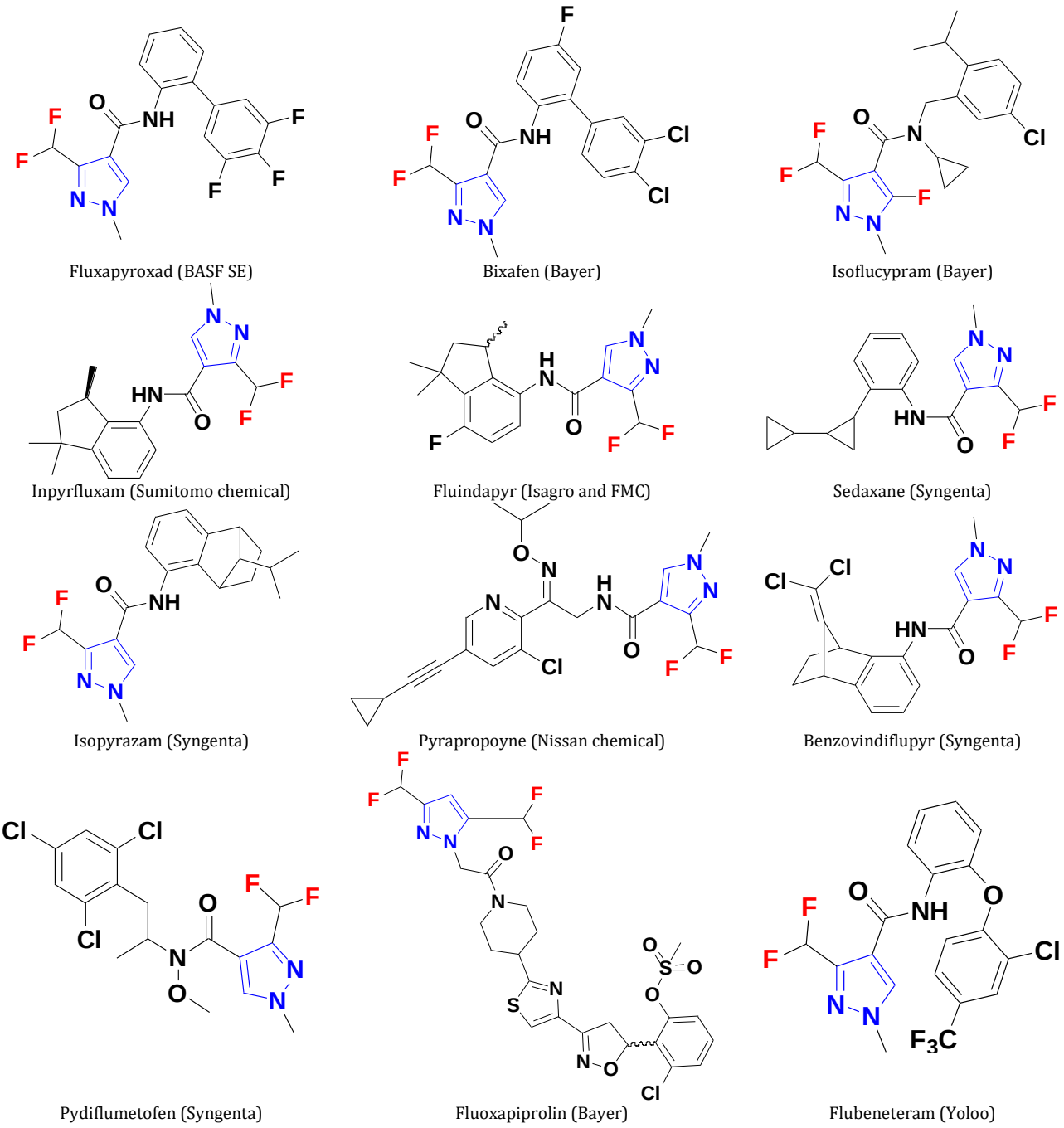


Fig. 1: Succinate dehydrogenase inhibitor fungicides containing fluoropyrazole

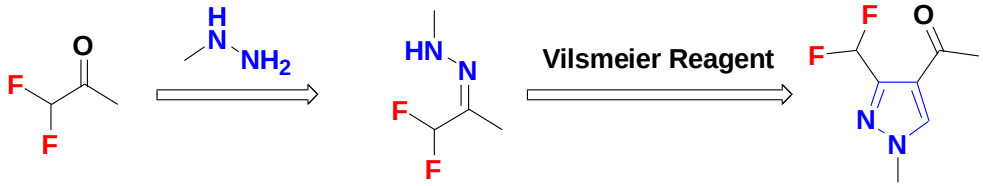


Fig. 2: Construction of fluorinated pyrazole ring by using 1,1-difluoro acetone

Regarding industrial preparation, 1,1-DFA can be prepared by reacting formaldehyde and 1,1-difluorochloroethane in an acid catalyst, usually sulfuric acid or p-toluene sulfonic acid. The reaction is exothermic, and the temperature is generally kept below 25 °C. Additionally, 1,1-DFA can be prepared by chemical reduction using sodium dithionite to reduce isobutyric acid with aqueous potassium hydroxide and catalytic amounts of palladium, copper, or zinc. This method is not generally suitable for large-scale industrial production since it cannot be carried out under conventional conditions. In addition, some studies have also reported alternative synthetic approaches for the industrial Preparation of 1,1-DFA. One method employed the reaction of chlorinated methyl derivatives with formaldehyde in tetrahydrofuran (THF) with acid catalysts. The response of methyl-3,3,3-trifluoro propionate and

formaldehyde in THF with p-toluene sulfonic acid in the presence of a base was reported to provide 1,1-DFA with a yield of 95% and selectivity of 95% (Deaton et al., 2021). This method can be scaled up. Another procedure also involves the reaction of isobutyric acid with diethyl carbonate and formaldehyde in the presence of a base. This method can provide 1,1-DFA with a yield of 96%, although it is unsuitable for large-scale industrial production. 1,1-DFA is widely used to synthesize drugs, agrochemicals, and other chemicals. Its industrial Preparation usually involves the reaction of formaldehyde and 1,1-difluorochloroethane or the chemical reduction of isobutyric acid. Various alternative synthetic approaches have also been reported, such as the reaction of chlorinated methyl derivatives with formaldehyde and the reaction of isobutyric acid with diethyl carbonate and formaldehyde. However, difficulties remain regarding scalability, cost-effectiveness, and selection of optimum catalysts. Therefore, developing further and optimizing the industrial Preparation of 1,1-difluoro acetone is significant.

The initial route report for synthesizing 1,1-difluoro acetone may date back to 1930, prepared from 4,4-difluoro acetoacetic acid ethyl ester. The step employed the hydrolysis of β-ketoacid ester, wherein a massive overdose of sulfuric acid and 4,4-difluoro acetoacetic acid ethyl ester in water provided 1,1-difluoro acetone in a low yield, as shown in Fig. 3. Over the next 90 years, based on the route mentioned above, more experts and scholars optimized relevant processes by changing acid environment, hydrolysis temperature, post-treatment measures, and other methods, and achieved some excellent results such as detailed impurity research and higher yield.

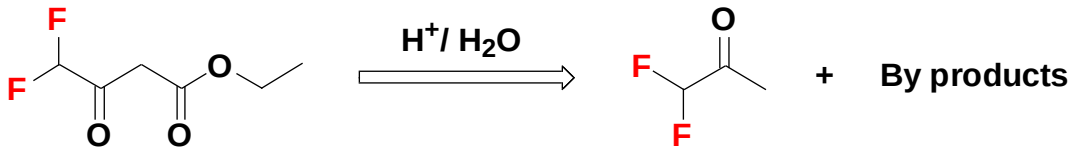


Fig. 3: Synthesis of 1,1-difluoro acetone by using 4,4-Difluoroacetoacetic acid ethyl ester

The synthetic route with 4,4-difluoro acetoacetic acid ethyl ester as the starting material shown in Fig. 3 is reasonable. Although the obtained product is a mixture of the target and by-product, it can be separated and purified by known engineering means to get qualified 1,1-difluoro acetone. The fly in the ointment is that due to hydrofluoroether's rising environmental protection cost, the current price of 4,4-difluoro acetoacetic acid ethyl ester has been high, significantly limiting the industrial application of this synthetic route. Deservedly, some artificial ways using other compounds as starting materials are recorded. 4,4-Difluoroacetoacetic acid diethyl ester yields 90%. Organic Synthesis follows nitration. This method involves acidic nitration reagents and hazardous organic nitro compounds. It's a risky, expensive synthesis procedure. Instead of 4,4-difluoro acetoacetic acid diethyl ester, the raw materials might be methyl ester. Trimethylphosphate and catalytic hydrogenation reduction may quickly synthesize 4,4-difluoro acetoacetic acid methyl ester and phenone: simple operation and moderate reaction conditions. Polycyclopentene impures the end product.

This technique relies on furan-2-carboxylic acid. Starch-like and non-toxic, it's beneficial. After oxidation and bromination, furan-2-carboxylic acid yields 4,4-difluoro acetoacetic acid diethyl ester. The reaction is simple and requires simply a reactor and distillation unit. This approach has two key downsides. First, response time is lengthy and uncontrollable. Second, the ester product yields poorly. Hydroformylation is another approach. The reaction is easy and produces 85% chemical. A rhodium catalyst is required, increasing raw material costs. There are many ways to make 4,4-difluoro acetoacetic acid ethyl ester, but they are expensive. The classic synthetic approach, esterification reaction, furan hydroxylation reaction, and hydroformylation reaction are all feasible. However, they all have substantial environmental protection costs or complex reactions.

3,3-Dichloro-1,1,1-trifluoropropan-2-one can be hydrogenated in the presence of 0.5% platinum/activated carbon at 110℃ to obtain a mixture of 1,1-difluoro acetone 1,1,1-trifluoro-2-propanone, 3-chloro-1,1,1-trifluoroacetone, as shown in Fig. 4.

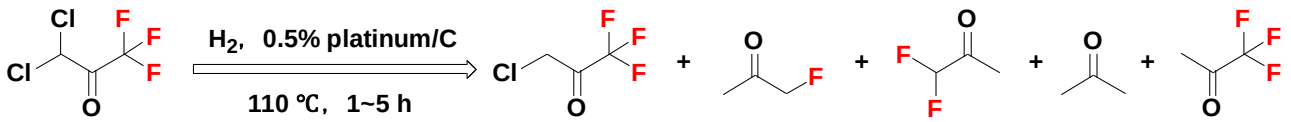


Fig. 4: Synthesis of 1,1-difluoro acetone by using 3,3-Dichloro-1,1,1-trifluoropropan-2-one

1,1-difluoro acetone can be prepared by Grignard Reaction of methylmagnesium bromide and ethyl difluoroacetate in dibutyl ether at 20℃, as shown in Fig. 5. 1,1-difluoro acetone can be obtained by fluorination of 1,1-dichloroacetate with fluorinating agents such as potassium fluoride and potassium hydrogen fluoride in diethylene glycol at higher temperatures (Marival-Hodebar et al., 1999)., as shown in Fig. 6.

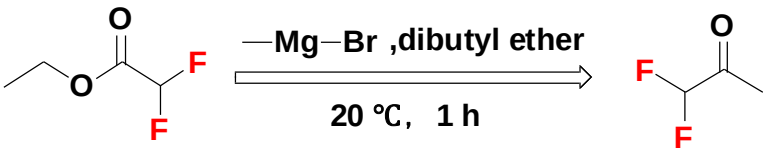


Fig. 5: Synthesis of 1,1-difluoro acetone by using ethyl difluoroacetate

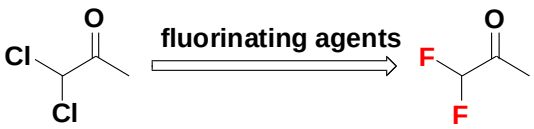


Fig. 6: Synthesis of 1,1-difluoro acetone by using 1,1-dichloroacetone

The synthetic routes shown in Fig. 4 to Fig. 6 describe some methods of preparing 1,1-difluoro acetone from relatively cheap raw materials such as 3,3-Dichloro-1,1,1-trifluoropropan-2-one, ethyl difluoroacetate, and 1,1-dichloroacetate, which reduce the manufacturing costs. However, it has the defects of high safety risk of Grignard Reaction, increased requirements for equipment corrosion resistance, high cost of waste gas treatment, and so on. The Preparation of 1,1-difluoro acetone from relatively cheap raw materials such as 3,3-Dichloro-1,1,1-trifluoropropan-2-one, ethyl difluoroacetate, and 1,1-dichloroacetate can be achieved through several methods which are both efficient and cost-effective. One of the methods of producing 1,1-difluoro acetone includes the Grignard reaction, which utilizes the highly reactive Grignard reagent to reaction 3,3-Dichloro-1,1,1-trifluoropropan-2-one, ethyl difluoroacetate and 1,1-dichloroacetate in a closed system. The reactants and the catalyst are placed in the design and heated at a temperature of about 180°C. After the reaction, a fine, colorless liquid of 1,1-difluoro acetone is obtained.

The reagents and reaction conditions used in the Grignard reaction approach are highly specialized and require expensive containment systems to prevent potential safety hazards. Additionally, the reaction running costs associated with this reaction are pretty high and not often feasible for industrial-scale production. A second method of preparing 1,1-difluoro acetone takes advantage of a much simpler reaction catalyzed by simple and commercially available catalysts such as sulfuric acid, ammonium sulfate, or phosphoric acid. This simple reaction begins with 3,3-Dichloro-1,1,1-trifluoropropan-2-one as well as ethyl fluoroacetate and 1,1-dichloroacetate as the starting materials, in the presence of one or more catalysts under specific temperature and pressure conditions. After the reaction, the products are filtered off, and the outcome of 1,1-difluoro acetone is recovered.

The simple catalyst reaction approach allows for an efficient and cost-effective route to 1,1-difluoro acetone synthesis, as it is generally much faster and more cost-efficient than the Grignard reaction. The reaction conditions are much more moderate than those required for the Grignard route; however, the final product quality may be slightly lower due to catalysts and other impurities. Additionally, the waste gases produced during this reaction must be carefully managed, as the presence of corrosive acids can become an issue. The two methods discussed have distinct advantages and disadvantages that should be considered when choosing a preparation technique for 1,1-difluoro acetone Synthesis from relatively cheap raw materials. The Grignard Reaction approach is suitable for industrial-scale production and can yield a high-purity product; however, it is more dangerous and expensive. The Catalyst approach is much less hazardous, cost-effective, and suitable for smaller-scale production, but the product purity may not be as high. Therefore, this paper focuses on solving the problem of expensive raw materials based on the synthetic route described in Fig. 3.

2. Experimental section

2.1. General methods

All solvents and raw materials are commercially available by industrial standards without special treatment. All operations are carried out in the air unless otherwise noted. The Preparation of ethyl 2,2-bromoacetate was improved based on public literature. In dichloromethane, ethyl 2,2-bromoacetate is prepared by reacting with sodium bromide. Ethyl 2,2-bromoacetate is inexpensive and readily accessible, and its reaction with sodium bromide in water yields a lot. This reaction is commonly catalyzed by zinc chloride. Input reactants, conditions, and solvent selection may enhance ethyl 2,2-bromoacetate production. To improve ethyl bromoacetate reactivation, use pentane to remove it from the aqueous solution. At 70–90° C and pH 6-7, ethyl bromacetate and sodium bromide may create ethyl 2,2-dibromoacetate. A good yield requires 1-2 hours of optimal reaction time.

Ethyl 2,2-dibromoacetate preparation requires a suitable solvent. DCM is the best solvent for ethyl bromoacetate deprotonation; thus, utilize it for this reaction. Tert-butyl bromide may also stabilize the reaction product (Loui and Schneider, 2022). The salt and catalyst used may improve ethyl 2,2-dibromoacetate preparation. Due to its lesser solubility in organic solvents, sodium bromide is a better counter-ion than potassium. Excess zinc chloride (1.2 equivalents) may also boost compound output. Optimizing each chemical step improves ethyl 2,2-dibromoacetate production. Consider the reactants, reaction conditions, solvent, and catalyst quantity. A non-volatile protecting group and an appropriate counter-ion may also boost ethyl 2,2-dibromoacetate production (Narender et al., 2006).

2.2. Synthetic route

Ethyl acetoacetate is first brominated to obtain Ethyl 2,2-dibromo acetate, followed by fluorine bromine exchange to obtain Ethyl 2,2-difluoro acetate, and finally degraded by 50% sulfuric acid solution to obtain the target product 1,1-difluoroacetone, as shown in Fig. 7. Schematic diagram of experimental equipment is shown in Fig. 8.

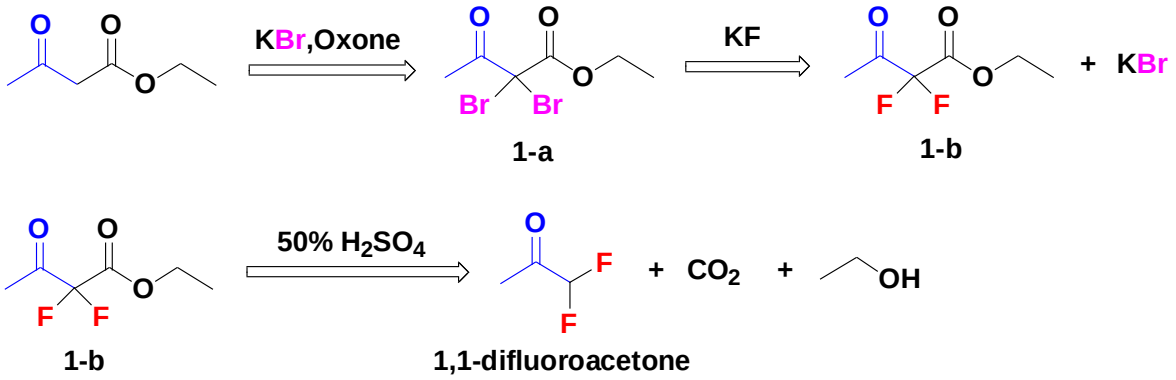
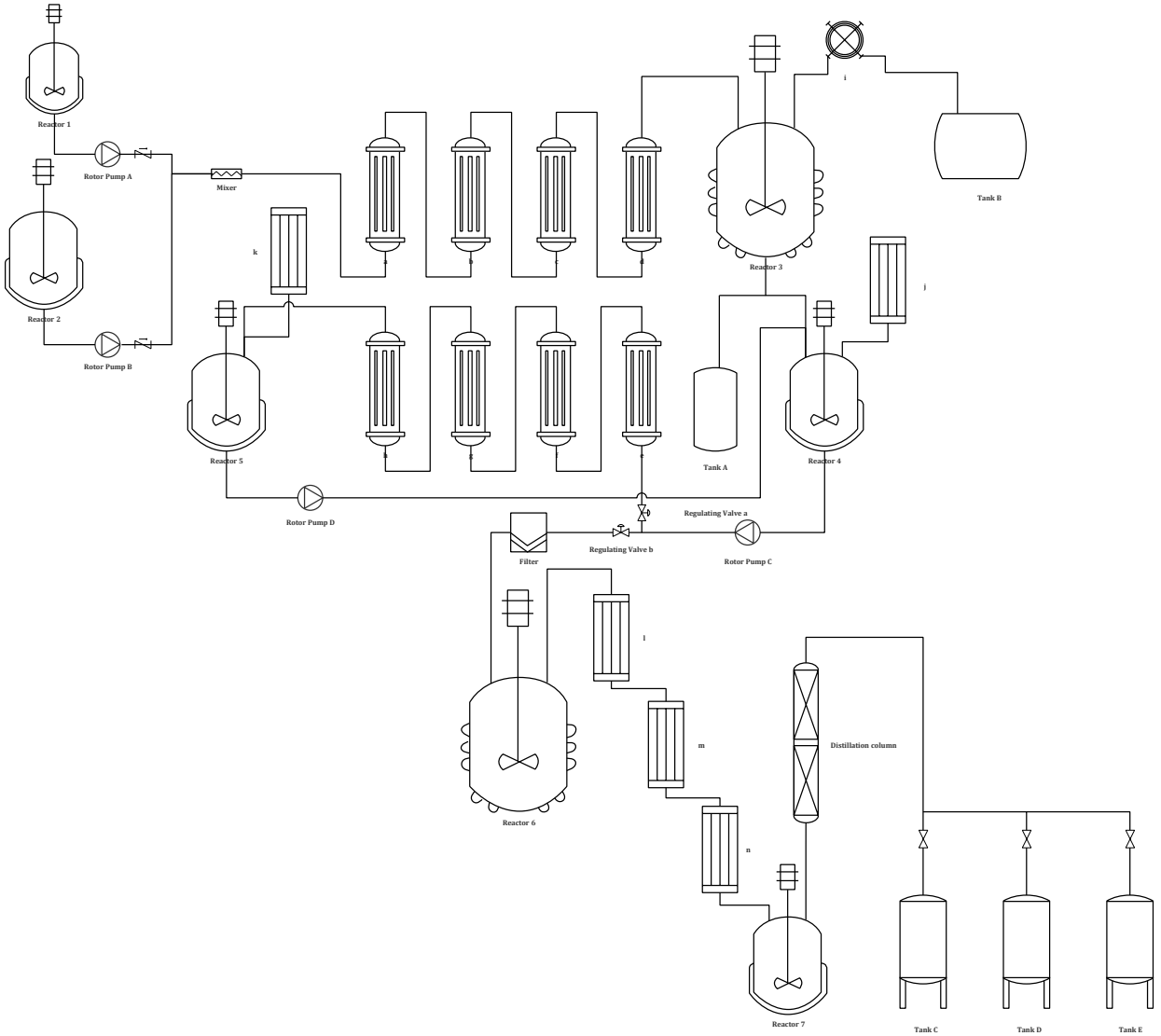


Fig. 7: Synthesis route of 1,1-difluoroacetone



Equipment parameters: Reactor 1 (volume: 2000 L, material: 316L); Reactor 2 (volume: 3500 L, material: 316L); Mixer (model: SK-68650, material: 904L); Tubular reactor a~h (model: 30 m2, material: SiC); Reactor 3 (volume: 5000 L, material: 409L); Spiral heat exchanger I (model: 45 m2, material: 904L); Tank A (volume: 2000 L, material: steel plastic-lined); Tank B (volume: 3000 L, material: steel plastic-lined); Reactor 4~5 (volume: 3000 L, material: 904L); Rotor pump A~D (material: Hastelloy, Flow: 6.5 m3/h, Lift: 32 m); Regulating valve a~b (material: Hastelloy); Filter (material: 316L); Condenser j~k (model: 15 m2 , material: 316L); Reactor 6 (volume: 5000 L, material: 316L); Condenser l~n (model: 15 m2, material: 316L); Reactor 7 (volume: 3000 L, material: 316L); Rectifying tower (model: DN200*25 m, material: 316L); Tank C~E (volume: 2000 L, material: 316L)

Fig. 8: Production equipment flow diagram

2.3. General procedure for the synthesis of 1,1-difluoro acetone

Ethyl 2,2-dibromo acetoacetate (1-a): Potassium bromide (600.00 kg, 5.04 mmol) was added to the well-stirred solution of ethyl acetoacetate (300.00 kg, 2.31 kmol) in n-heptanol (200 L) and the reaction mixture was allowed to stir at room temperature in Reactor 1. Reactor 2 was charged with oxone (3100.00 kg, 5.04 kmol) and n-heptanol (1000 L) then the mixture was stirred sufficiently so that oxone was evenly dispersed in n-heptanol. The feed liquids in Reactor 1 and Reactor 2 were pumped into the mixer with the appropriate flow by their respective rotor pumps at the same time. The outlet of the mixer was connected with four tubular reactors in series. When the feed liquids passed through Tubular reactor a~d with the progressive rise of stated temperature (a: 60~65℃, b: 80~85℃, 95~100℃, 105~110℃), ethyl acetoacetate was gradually brominated, and the dibromide (1-a) was temporarily stored in the Reactor 3 and cooled to below 60℃ to prepare for the following process.

Water (1000 L) was added to Reactor 3 at a temperature not exceeding 60℃ to dissolve much of the potassium persulfate produced by the reaction. After adding water, stand for 30 minutes to separate the solution. The water layer was a potassium persulfate solution, and the organic layer was the n-heptanol solution of dibromide (1-a). The organic layer was washed with water (500 L) again, and the washed organic layer was distilled to 110℃ in Reactor 3 to evaporate the water residual in the organic layer.

1,1-difluoro acetone: The reaction mixture in Reactor 3 was transferred to Reactor 4 by gravity, then potassium fluoride (300.00 kg, 5.16 kmol) was added and stirred evenly, and the homogeneous suspension was heated to 150℃. When the temperature in Reactor 4 rose to technological requirements, the mixture was continuously circulated between Reactor 4, Tubular reactor e~h, and Reactor 5 via the Rotor pump C~D. After the eighth, the combination turned black, and the dibromide (1-a) was completely fluorinated into difluoride (1-b). After G. C. analysis showed the complete consumption of dibromide (1-a), the reaction liquid in Reactor 4 was slowly transferred to Reactor 6 containing 50% H2SO4 at 90℃ through the Filter with Rotor pump C. The filter cake was KBr (recycled after refining). The filtrate was hydrolyzed and decarboxylated immediately when it contacted the sulfuric acid solution. The carbon dioxide, 1,1-difluoro acetone, and a small amount of ethanol that escaped from Reactor 6 were condensed by the Condenser l~n and then collected in Reactor 7. While the feed liquid of Reactor 4 was emptied, the hydrolysis and decarboxylation of difluoride (1-b) were expected to be completed.

The residue in Reactor 6 was a mixture of n-heptanol, water, sulfuric acid, ethanol, and inorganic salt, which can be recycled after membrane separation. The fraction collected in Reactor 7 was a mixture of 1,1-difluoro acetone, a small amount of water, and ethanol. Pure 1,1-difluoro acetone can be obtained by rectification and collected in Tank C. Tank D collected a variety of little 1,1-difluoro acetone, water, and ethanol, which was incorporated into the next batch of the rectification process. Tank E contained a mixture of water and ethanol, which will be subject to biochemical treatment or recovery of ethanol depending on the COD value.

The 1,1-difluoro acetone collected in Tank C was analyzed, and the results showed that the content of G. C. was 99.60%, and the moisture content of Karl Fischer was 0.18%. Colorless liquid (91.25% Yield).

Note: The temperature in the Reactor 5 and Tubular Reactor e~h is controlled at 155~160℃. The regulating valve a~b is utilized to switch the direction of feed liquid and can be closed entirely when needed.

3. Results and discussion

3.1. Effect of feeding ratio on reaction results

According to the well-known knowledge of the public, alpha position hydrogen of ethyl acetoacetate can be brominated easily, and the potassium oxone/KBr reagent combination is an efficient and environment-friendly bromination reagent. The possible reaction mechanism is shown in Fig. 9.

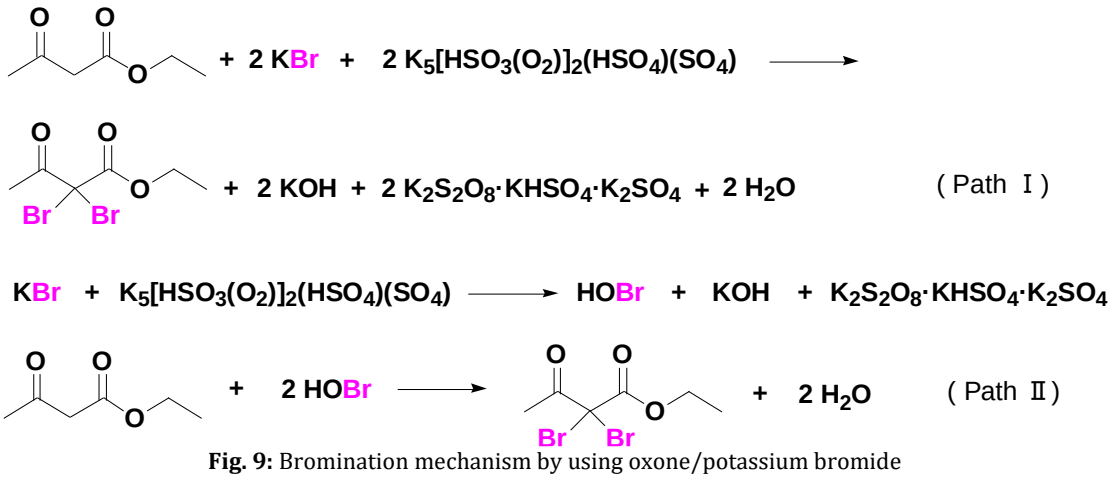
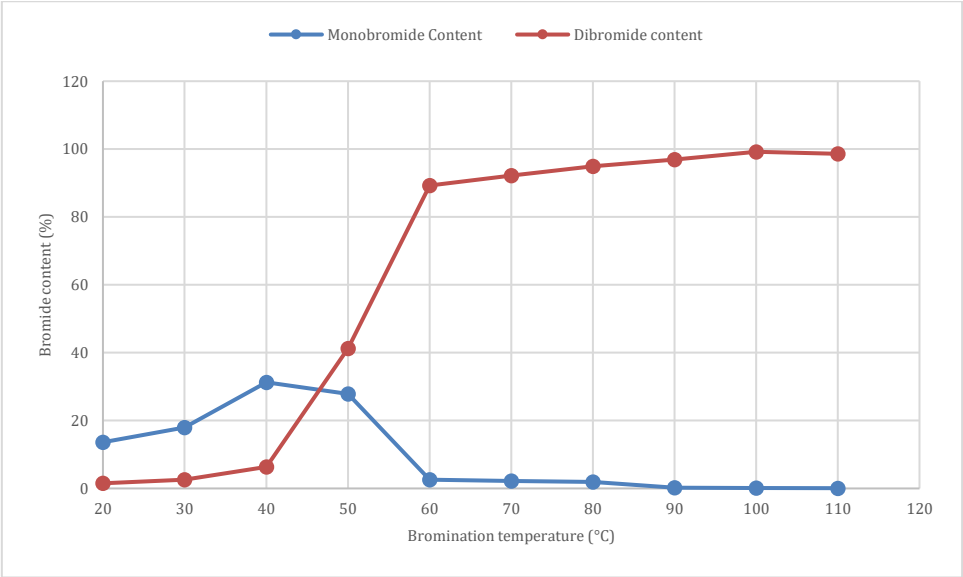
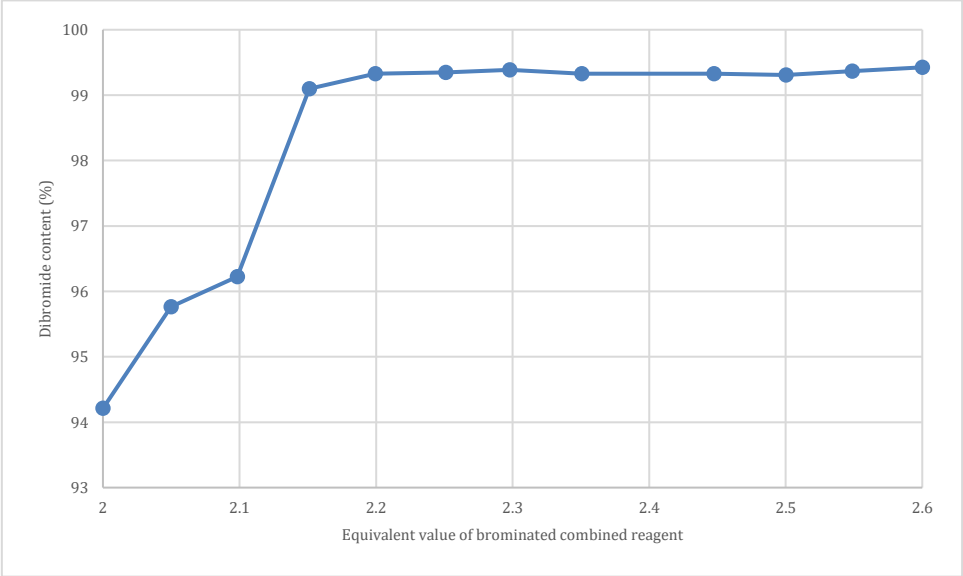


Fig. 9: Bromination mechanism by using oxone/potassium bromide

From Fig. 9, it appears that at least two equivalents of KBr and two equivalents of oxone are needed to replace the two alpha hydrogen atoms of ethyl acetoacetate completely with bromine atoms in theory (Shuchi et al., 2021). Considering that the ethyl acetoacetate not involved in the reaction will bring difficulties to subsequent separation, the main thing is to confirm the optimal reaction temperature under atmospheric pressure from 2.5 equivalent oxone/KBr (Zhu et al., 2022). The bromination result of ethyl acetoacetate under various reaction temperature conditions is shown in Fig. 10a. It is evident from Fig. 10a that the bromination process remains at the monobromide stage when the temperature is lower than 50°C, and the content of monobromide decreases (Mani et al., 2021). Meanwhile, the dibromide (1-a) content increases with the increase in bromination temperature (higher than 60°C) (Prajapat and Gogate, 2019). Based on this result, the bromination temperature will be optimized with relevant practical experience, heat transfer economy, and industrial operability (Wang et al., 2020). Furthermore, keep it unchanged at a reaction control temperature of 80°C and conduct the comparison experiments under different dosages of brominated combined reagent (Li et al., 2019); the result is shown in Fig. 10b.



(a) Bromide content at different bromination temperatures



(b) Dibromide content under different dosages of brominated combined reagent

Fig. 10: Bromination results under different bromination conditions

In summary, the dosage of bromination combined reagent is preferably 2.2 equivalent, and the bromination temperature will be optimized in the range higher than 60°C combined with engineering practice experience.

Note: (a) Although fluorine bromine exchange reaction is not as common as fluorine chlorine exchange reaction because of the higher price of bromine, it is also a conventional chemical reaction (Tyutereva et al., 2021). Therefore, this paper will refer to the traditional fluorine chlorine exchange means for the fluorine bromine exchange experiment. (b) Difluoride's acid hydrolysis and decarboxylation (1-b) do not consume sulphuric acid

with lower economic value (Azeez et al., 2018). Therefore, the feeding amount of the hydrolysis and decarboxylation process shall be subject to the convenience of complete conversion and post-treatment; no further optimization experiment shall be conducted (Hsu et al., 2002).

3.2. Suggestion on the whereabouts of Oxone degradation products

From the mechanism of oxone oxidative bromination described in Fig. 9, one of the main degradation products produced by oxone oxidation of KBr is potassium persulfate, which is a water-soluble initiator that can be developed to replace azodiisobutyronitrile, a reagent used for photodegradation, a promoter used for the n-nitrosation, an adjuvant to degradation and so on. In addition, an actual application of potassium persulfate is for the nitration of aromatic compounds with safety, good functional group tolerance, and no acid waste, a scorching topic in the field of C-H bond activation in recent years. The relevant reaction equation is shown in Fig. 11.

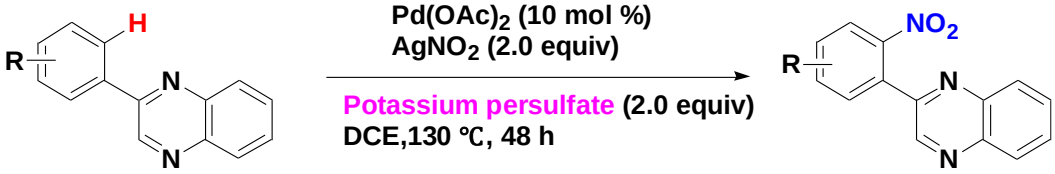


Fig. 11: Nitrification of aromatic compounds by using potassium persulfate

According to the above introductions, potassium persulfate, the degradation product of oxene, is widely used (Lin, 2001). We strongly recommend developing it as a product for the nitration of aromatic compounds in the field of C-H bond activation.

3.3. Validation of stage of tubular reactor on reaction results

A tubular reactor with a high aspect ratio is commonly used in the chemical industry, whose structure can be a single tube or multiple tubes in parallel, empty lines, or filled with granular catalysts (Zhang et al., 2013). Compared with the structure of the tubular reactor, the stage of the tubular reactor has more influence on the reaction results in the industry because there are many standard tubular reactors on the market.

In this paper, the stage of the tubular reactor in the bromination process is validated by the degree of bromination. For example, when the central control result of the reaction liquid at the outlet of the fourth stage tubular reactor meets the requirements, it is acknowledged that the stage of the tubular reactor is four (Franco et al., 2012). In turn, the location of the tubular reactor involved in the fluorination process is determined by analogy. Bromination involves adding bromine molecules to a product to change its structure, yielding beneficial chemical and physical qualities (Korbahti and Tanyolac, 2009). Bromination may be done by reacting bromine gas or, most often, a bromine solution in water or alcohol. The bromine-containing substance breaks down and reacts with the substrate to create a brominated product (Lindén et al., 1998). The reactants combine as they flow through a tubular reactor, causing the chemical reaction. As reactants flow through the tubular reactor, they encounter additional catalysts and bromine, increasing bromination (Miskolczi et al., 2010). The output stream bromine concentration determines bromination.

The exit stream's bromination determines the tubular reactor's phases. Each step of the tubular reactor achieves a specified bromination level. Chemical reactions intensify when reactants travel through stages (Memon et al., 2022). Thus, higher reactor stages increase output stream bromination. The desired bromination level and product attributes dictate the tubular reactor's stage count. The tubular reactor is an efficient bromination reactor that maximizes selectivity and reactivity and reduces reaction steps. To get the required outcomes, tubular reactors are designed with reaction temperature, pressure, and catalyst reactivity in mind.

Monitoring the tubular reactor stages optimizes bromination. To achieve the required bromination in each tubular reactor stage, evaluate the reactants, catalyst, and reaction parameters. Reactants must be monitored for purity, concentration, reaction temperatures, and pressures. After bromination, the exit stream bromine concentration may be measured to determine the degree of bromination in each step of the tubular reactor. If the central control result of the reaction liquid at the exit of each stage fulfills the criteria, the tubular reactor stage did its duty. Finally, the fluorination process's tubular reactor stage may be calculated using the same approaches.

3.4. Discussion on the conditions of hydrolysis and decarboxylation

β-Ketoacid esters are compounds containing keto carbonyl groups in their β-positions, which can be used for the Synthesis of chiral amine, catalyst-free direct nitration, highly enantioselective allenylation, etc., and they can be hydrolyzed then decarboxylated to produce ketone, carbon dioxide, and alcohol (Borges et al., 2021). The difluoride (1-b) in this paper is a typical β-Ketoacid ester, which can be

hydrolyzed and then decarboxylated in sulfuric acid solution to produce 1,1-difluoro acetone, carbon dioxide, and ethanol (Buß et al., 2018). Therefore, the possible reaction conditions affecting the reaction results may be a sulfuric acid concentration, dosage of the sulfuric acid solution, and reaction temperature.

Because there are latent safety risks in using concentrated sulfuric acid and sufficient 50% sulfuric acid on the market for sale, we first used 50% sulfuric acid to investigate the results of hydrolysis and decarboxylation and achieved satisfactory results (Han et al., 2022). The dosage of sulfuric acid is described in Section 2.1. So, we focused on the effect of reaction temperature on hydrolysis and decarboxylation.

We add the reaction mixture of fluorination (n-heptanol solution of difluoride (1-b) containing a small number of inorganic salts) to 50% sulfuric acid solution at different temperatures at an appropriate rate (equipped with a condenser to prevent volatile components except for carbon dioxide from escaping from the reaction mixture). The optimal reaction temperature is selected by analyzing the residual difluoride (1-b) in the reaction mixture (Han et al., 2022). The results show that the reaction can be completed when the temperature exceeds 55℃. To achieve the sound effect of separating the target product from the reaction mixture while reacting and to improve the feeding speed, we finally raised the reaction temperature to 90℃, which is in line with the requirements of industrial production.

4. Conclusions and discussion

The bromination of the two α-Hs of ethyl acetoacetate using the oxone/KBr system effectively takes place under specified conditions. For optimal outcomes, the reaction temperature should exceed 60℃, with atmospheric pressure maintained. The determined optimal brominating agent equivalence is 2.2. Underutilizing this brominating agent results in an incomplete reaction of ethyl acetoacetate, complicating the separation process and escalating the costs involved. However, beyond the highlighted parameters, increasing temperature and pressure does not significantly enhance the outcome. Hence, the delineated conditions provide a balanced, economical, and efficient approach.

Comparatively, ethyl 2,2-dibromo acetoacetate (1-a) undergoes a fluorine bromine exchange reaction with potassium fluoride in n-heptanol, yielding difluoride (1-b) and KBr. This product doesn't necessitate further purification before its subsequent application. Concurrently, refining and reusing KBr from the mixture can offer a sustainable method, cutting down both production expenses and environmental waste.

For the hydrolysis and decarboxylation phases, the application of a sulfuric acid solution at 90℃ ensures the timely release of the target, 1,1-difluoro acetone. Upon rectification, a high-quality colorless product emerges, boasting an impressive yield of 91.25%. Given the potential hazards linked with concentrated sulfuric acid, utilizing commercially available 50% sulfuric acid is advisable, especially when it delivers satisfactory outcomes.

Intriguingly, tubular reactors, when employed in the bromination and fluorination stages, markedly enhance production efficiency. A salient aspect of this methodology is its resourcefulness: bromine atoms are retained throughout, and introduced fluorine atoms via potassium fluoride are incorporated into the desired product. This strategy, now implemented by a Chinese chemical enterprise, is poised for broader industrialization given its operational simplicity, cost-effectiveness, safety, eco-friendliness, and controlled post-treatment process.

Drawing parallels with existing methodologies, the proposed production process of 1,1-difluoro acetone undoubtedly stands out. The potential ramifications of this approach are vast. With a cost-efficient and environmentally conscious methodology, it's plausible that this route could drive down the prices of related succinate dehydrogenase inhibitor fungicides containing fluoropyrazole ring. As a likely result, farmers could benefit immensely, both economically and in terms of enhanced crop protection. Looking forward, the promotion of this approach could revolutionize fungicide production, positioning it as a sustainable and cost-effective pillar in the agricultural sector.

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Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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