



Research Article

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Application of phase transfer catalyst in the synthesis of cyhalofop butyl

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ABSTRACT

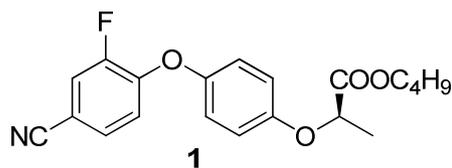
R-(+)-2-(4-hydroxyphenoxy) propionic acid reacted with 3, 4-difluorobenzonitrile at 80°C in DMF gave (R) -2-[4-(4-cyano-2-fluorophenoxy) phenoxy] propionate potassium, which was esterified with butyl bromide to afford Cyhalofop butyl. The phase transfer catalyst tetrabutylammonium bisulfate catalyzed the reaction efficiently; the total yield was obtained 94.2% with 96% chemical and 98% e.e optical purity respectively

Keywords: Cyhalofop butyl; Phase transfer catalysis; Tetrabutylammonium bisulfate; Synthesis

INTRODUCTION

With the development of modern agriculture, herbicides are widely used to inhibit the growth of weed that hurts the crops and reduces the production. Cheap herbicides with high efficiency and good security are universally needed for the large scale planting. The research and development of herbicide is an important field in modern chemistry. The low toxicity, low loading amount, low residual, high selectivity and readily biodegradable are the orientation of all the pesticide. So popularizing the herbicides varieties with excellent performance to alternative environmentally destructive species is long endeavors [1]. A probably way that can enhance the production is to reduce the cost of production.

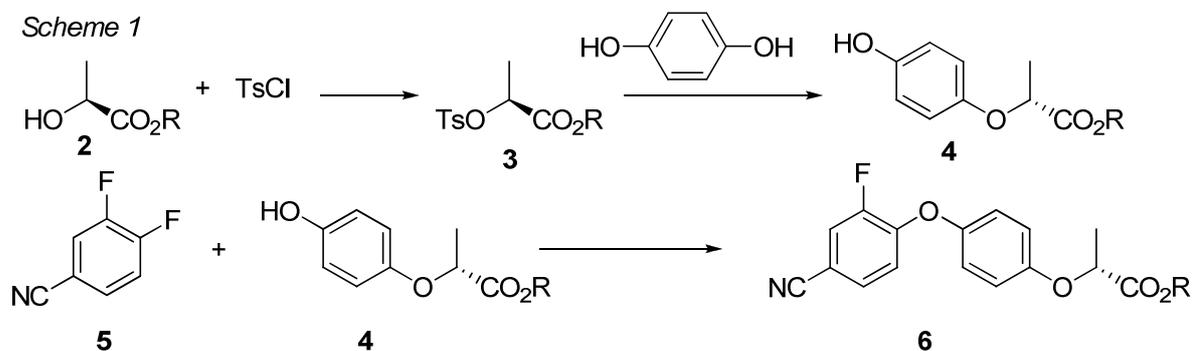
Cyhalofop-butyl, which is tradenamed Clincher, is developed by Dow Agricultural Sciences Corporation and used as postemergence herbicide for paddy. It is mainly used for the controlling of most of gramineous weeds especially for paddy serious harm *Leptochloa* those other agents currently still less effective. Cyhalofop-butyl has shown excellent selectivity on rice plants. The chemical name of Cyhalofop-butyl is butyl (R) -2-[4-(4-cyano-2-fluorophenoxy) phenoxy] propionate with a structure described below:



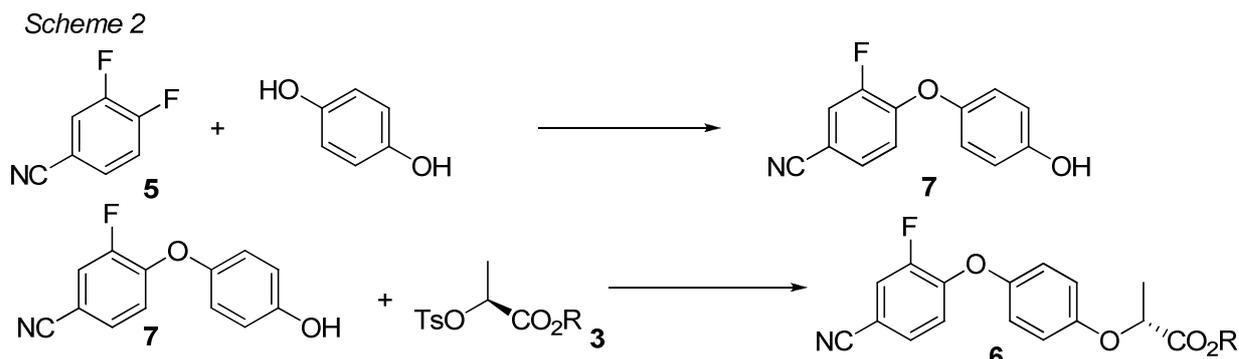
As a novel acetyl coenzyme A carboxylase inhibitor, Cyhalofop-butyl is a low-toxic non-carcinogenic herbicide, and has no stimulating effect on the skin, no teratogenic and mutagenic effects, only has slight irritation to the eyes. Cyhalofop-butyl shows high activity and excellent selectivity for the killing of weeds with the advantage of low toxicity and residual. Because the loading amount is extraordinary small, Cyhalofop-butyl is regarded as a high efficient, environmental benign and safe herbicide as it is mildly hydrolyzed under neutral or weak acid environment [2], Cyhalofop-butyl is a chiral fluorinated farm chemicals that comply with the trend of pesticide [3, 4], so it will gain more

and more concern in the future. Nowadays, a lot of pesticide dosage forms that depended on Cyhalofop-butyl have been developed, and even Cyhalofop-butyl itself including production, storage, transportation and application is also being studied deeply [5].

According to the literatures, the synthesis of Cyhalofop-butyl is mainly achieved through the following routes: Luo and coworkers reported a synthetic route that (S)-methyl lactate reacts with toluene-4-sulfonyl chloride to give (S)-methyl 2-(tosyloxy) propionate, which reacts with hydroquinone to obtain (S)-methyl 2-(4-hydroxy-phenoxy) propionate. The latter condensates with 3, 4-difluorobenzonitrile, then after hydrolysis and esterification with butanol the target product Cyhalofop-butyl **1** is obtained with 49% yield (Scheme 1) [6, 7].



In another report, the hydroquinone reacts with 3, 4-difluorobenzonitrile to give 3-fluoro-4-(4-hydroxyphenoxy)-benzonitrile, then reacts with (S)-alkyl 2-(tosyloxy) propionate to afford Cyhalofop-butyl (Scheme 2) [8].



In a recent report, Cyhalofop-butyl is obtained from the condensation between (R)-2-(4-hydroxy-phenoxy) propanoic acid then alkylation with butyl bromide. This improvement cut down several synthetic steps from as shown in Scheme 1, but the operation conditions is still harsh for the expensive solvent acetonitrile should be used and high temperature and pressure are necessary [9].

In each reported route, 3, 4-difluorobenzonitrile is a key starting substance that covers the most cost of production [10]. So we think the first synthetic route as shown in *Scheme 1* is worthy to be studied deeply because expensive 3, 4-difluorobenzonitrile will be lost less during the production process than in another route as shown in *Scheme 2*. To improve the conversion of 3, 4-difluorobenzonitrile **5**, high reaction temperature of the condensation between **4** and **5** is usually beneficial. But when the condensation is carried out at high temperature under alkaline condition, there is another problem that is racemization. As a chiral pesticide, qualified Cyhalofop-butyl must have sufficient optical purity, so excellent enantiomer selectivity is essential for the synthesis. In order to achieve good conversion and good chiral selectivity at the same time, high-performance catalyst will be important. Through our investigations, we have found that phase transfer catalyst promoted this reaction efficiently. With the introduction of alkyl quaternary ammonium as catalyst, we have synthesized Cyhalofop-butyl with good yield and high optical purity.

EXPERIMENTAL SECTION

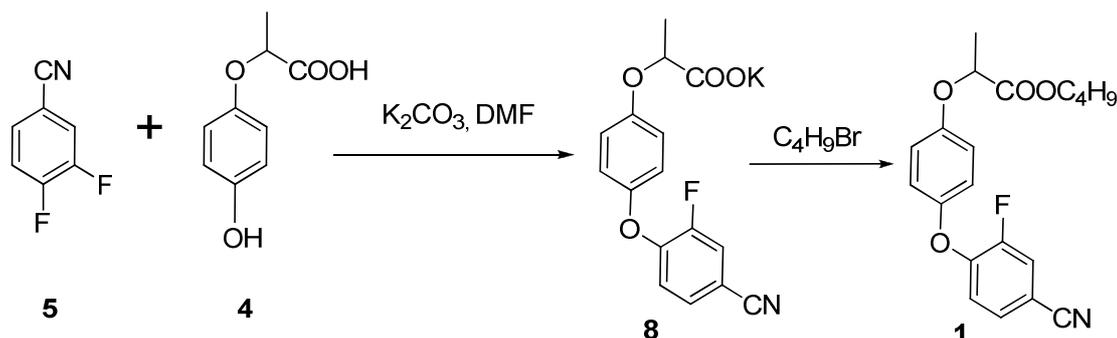
Typical procedure: (R)-2-(4-hydroxy-phenoxy) propanoic acid 546.5 mg, 3, 4-difluorobenzonitrile 417.3 mg, anhydride potassium carbonate 974.4 mg, tetrabutylammonium bisulfate and DMF (N, N-dimethyl formamide) 4 mL were added in a sealed tube then heated at 80 °C for 7 hours under stirring. After the completion of the condensation, the reaction mixture was cooled to 50 °C and then butyl bromide 1.233 g was added. The tube was then sealed again and

heated at 80 °C for 6 h. The solvent and excess butyl bromide were recovered under reduced pressure, the residual was then extracted with 3×20 mL of ethyl acetate. The collected organic phase was evaporated to give the target product as colorless oil that solidified after long time storage at room temperature. The total yield was 94.2 % with 96% purity (HPLC). The optical purity was determined 98% e.e with methanol as reference.

RESULTS AND DISCUSSION

To explore the optimized conditions of the condensation between 3, 4-difluorobenzonitrile and (R)-2-(4-hydroxy-phenoxy) propanoic acid, a series of experiment were carried out under various conditions including different catalysts, temperatures and solvents. The results are listed in Table 1.

Table 1. The condensation conditions in the Cyhalofop-butyl synthesis ^a



Catalyst	Solvent	Temp [°C]	Yield [%]	e.e [%] ^b
none	DMF	80	72	-
N(Bu) ₄ HSO ₄	DMF	80	94	98
N(Bu) ₄ Br	DMF	80	92	92
TEBA	DMF	80	92	95
N(Bu) ₄ HSO ₄	DMAc	80	84	-
N(Bu) ₄ HSO ₄	acetonitrile	80	70	-
N(Bu) ₄ HSO ₄	chlorobenzene	80	12	-
N(Bu) ₄ HSO ₄	toluene	80	10	-
N(Bu) ₄ HSO ₄	DMF	70	67	-
N(Bu) ₄ HSO ₄	DMF	100	95	95
N(Bu) ₄ HSO ₄	DMF	80	82 ^c	-

^a 3 mmol of **4**, **5**, 7 mmol of K₂CO₃, 0.15 mmol of catalyst, 4.0 mL of solvent, 9 mmol butyl bromide were added. ^bNo optical examine was carried out when the yield is less than 90%; ^c 6 mmol of butyl bromide was added;

In the absence of catalyst the Cyhalofop-butyl is obtained with 72% yield in the reaction that **4** condensed with **5** in K₂CO₃/DMF at 80 °C then alkylated with triple amounts of butyl bromide. But in the present of tetrabutylammonium bisulfate, tetrabutylammonium bromide (TBAB) or triethyl benzylammonium chloride (TEBA) as catalyst, excellent yields of >90% are achieved. This indicates that phase transfer catalyst can promote the reaction efficiently. However, the products obtained from different catalyst have shown different optical purity. The tetrabutylammonium bisulfate gives the best chiral selectivity of 98% e.e, while TEBA gives 95% e.e and TEBA gives only 92% e.e. selectivity. That may because the nucleophilicity of catalyst anion leads to a slight racemization. The bisulfate ion has the weakest nucleophilicity amount the catalyst anion, so it gives no obvious racemization and the optical purity in the case of tetrabutylammonium bisulfate used as catalyst is commercially permitted. In other cases and even in the absence of catalyst, further purification is usually needed to improve the chiral purity.

To investigate the best conditions of the catalytic reactions, experiments with various solvents and temperature were carried out. It is found that non-proton polar solvent is helpful to the condensation. Among these solvents, DMF, DMAc, and acetonitrile make the reaction proceeded smoothly with good to excellent yield, while neither chlorobenzene nor toluene gives more than moderate yield. As reported [9], the condensation can not achieve high conversion in acetonitrile at low temperature such as 80 °C and in the absence of catalyst.

The reaction temperature is another key factor. When the reaction temperature is low to 70 °C, only 67% yield is obtained. To improve the conversion, the reaction must be carried out at high enough temperature. But high temperature will cause racemization in the alkaline conditions that is necessary for the condensation. When the reaction is proceeded at over 100 °C, the optical purity descends. So an optimized temperature is 80 °C for the catalytic reaction to obtain the excellent chiral selectivity of 98% e.e.

In the last step, three folds amount of butyl bromide was added to achieve the alkylation that formed the butyl ester. We tried less loading amount of butyl bromide, but failed. Two folds amount of butyl bromide gave only 82% yield of Cyhalofop-butyl. Moreover, excess butyl bromide can be recovered by simple distillation after the reaction so it will not be wasted.

CONCLUSION

In summary, Cyhalofop-butyl is synthesized by condensation between 3, 4-difluorobenzonitrile and (R)-2-(4-hydroxy-phenoxy) propanoic acid and then esterification with butyl bromide in one pot. Tetrabutylammonium bisulfate is an excellent catalyst for the key condensation step. This method has advantage of mild conditions, high yield and excellent optical purity, and the easy to handle. This can be easily moved to industrial application.

Acknowledgement

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