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ORIGINAL PAPER

KI-catalysed synthesis of 4-methylcatechol dimethylacetate and fragrant compound Calone 1951®

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Synthesis of the fragrant compound Calone 1951® from 4-methyl catechol and methyl bromoacetate entails three successive reactions: the Williamson reaction, Dieckmann condensation, and hydrolysis–decarboxylation reaction. In this paper, the synthesis of 4-methylcatechol dimethylacetate (MCDA) via the Williamson reaction by adding KI as catalyst was investigated. It was found that the addition of an appropriate amount of KI can significantly increase the product yield due to generation of methyl iodoacetate via the reaction between KI and methyl bromoacetate. The synthesised MCDA as well as Calone 1951® were first characterised by melting points, HPLC, IR, and NMR analyses. Next, the effect of the key operating factors on MCDA synthesis by the Williamson reaction was investigated and the optimum operating conditions were obtained via a group of orthogonal experiments. The verification experiments demonstrated that, under the optimum operating conditions, the MCDA yield could be increased from 78.5 % to 95.4 % by the addition of an appropriate amount of KI; the corresponding yield of Calone 1951® increased to 68 %.

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Keywords: 4-methylcatechol dimethylacetate, MCDA, KI, catalysis, Calone1951® synthesis, synthesis process

Introduction

Calone 1951®, 7-methyl-2*H*-benzo-1,5-dioxepin-3(4*H*)-one, is a member of the benzodioxepinone family with a pleasant fragrance redolent of watermelon (Drevermann et al., 2005). The synthesis of Calone 1951® reported in the literature can be categorised into four procedures according to the starting materials. The starting materials for the first procedure are 4-methylcatechol and chloroacetonitrile (Rooney et al., 1975), from which Calone 1951® is synthesised via consecutive etherification, condensation, and acidification reactions with the product yield as high as 51 %. The second procedure starts from 4-methylcatechol and 1,3-dichloro-2-propanol (Rosnati & De Marchi, 1962), from which 7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-3-ol is first synthesised, then oxidised to Calone 1951®. The product yield achieved by this procedure is low (4 %). In the third procedure, Calone 1951® is synthesised from 4-methylcatechol and 1,3-dichloroacetone via a cyclic condensation and a rearrangement reaction, successively (Shi, 2006; Zhang, 2010; Lin et al., 2009). This procedure can achieve a product yield of 50 %. However, 1,3-dichloroacetone is highly toxic and corrosive. The fourth procedure for synthesising Calone 1951® starts from 4-methylcatechol and methyl bromoacetate (Drevermann et al., 2005, 2007a, 2007b; Beere-

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*Corresponding author, e-mail: lcdong72@cqu.edu.cn boo et al., 1970; Qiao, 2009) via sequential Williamson reaction, Dieckmann condensation, and hydrolysis–decarboxylation reactions with Calone 1951® yield as high as 57 %.

In the procedure to synthesise Calone 1951® from 4-methylcatechol and methyl bromoacetate, synthesis of the first intermediate, 4-methylcatechol dimethylacetate (MCDA), via the Williamson reaction is a process of nucleophilic substitution, the efficiency of which depends on the activity of the alkylating reagent. It is well known that the activity of the alkylating reagent is related to its halogen atom and iodides usually have a higher activity than bromide in alkylation reactions (Miao et al., 2006; Dong et al., 2011; Fujita et al., 2001; Wang & Lee, 2007; Varszegi et al., 2008). As a consequence, methyl iodoacetate is a better alkylating agent than methyl bromoacetate. However, methyl iodoacetate is expensive and unstable so it cannot be used directly in the synthesis reaction. Accordingly, in this study, methyl bromoacetate was used as the alkylating agent, while potassium iodide (KI) was added as catalyst in the Williamson reaction. In the reaction, KI reacts with methyl bromoacetate to generate methyl iodoacetate via a substitution reaction, which further reacts with 4-methylcatechol to produce MCDA. As methyl iodoacetate is more reactive than methyl bromoacetate, the MCDA yield can be significantly increased by the addition of KI.

In this paper, the structure and purity of the synthesised MCDA and Calone 1951® were characterised by using the melting point measurement, IR, HPLC and NMR analyses. Next, the effect of the several key operating factors on the Williamson reaction was investigated and the optimum operating conditions were obtained via a group of orthogonal experiments.

Experimental

Materials and methods

4-Methylcatechol was purchased from Shanghai Energy Chemical Institution (Shanghai, China); methyl bromoacetate was purchased from Jiangsu Dongtai Xinyuan Chemical Co. (Wuxi, China). Potassium tert-butoxide (KO^tBu) was purchased from Chengdu Kelong Chemical Institution (Chengdu, China). KI, K_2CO_3, acetone, tetrahydrofuran (THF), and anhydrous ethanol were all obtained from Chongqing Chuandong Chemical Co. (Chongqing, China). All the reagents were of analytical grade, except for acetone, which was dried over anhydrous sodium sulphate (Na_2SO_4), and THF, which was dried over calcium hydride (CaH_2); the other reagents were used without further purification.

Melting points were measured using an X-5 microscopic melting point detector (Beijing Focus Instrument Co., Beijing, China). IR spectra of the compounds dissolved in $CDCl_3$ were recorded on a Nicolet MAGMA-IR550 spectrometer (Nicolet Instrument, Madison, WI, USA) using KBr pellets. The ^1H NMR and ^{13}C NMR spectra of the synthesised MCDA and Calone 1951® dissolved in $CDCl_3$ were recorded on a Bruker AV 500 NMR spectrometer (Bruker, Ettlingen, Germany) using tetramethylsilane (TMS) as internal standard.

HPLC chromatograms of the synthesised products were analysed using an Agilent 1100 HPLC system (Agilent Technologies, Santa Clara, CA, USA), equipped with a Diamonsil C_{18} (4.6 mm × 150 mm × 5 µm) column and UV 100 detector. The operating conditions for MCDA analysis were: injection volume: 20 µL; concentration of the injection solution: 0.0266 g L^{-1}; eluent: methanol–water ($\varphi_r = 50 : 50$); flow-rate: 0.8 mL min^{-1}; UV detecting wavelength: 282 nm. The operating conditions for Calone 1951® analysis were: injection volume: 10 µL; concentration of the injection solution: 0.0530 g L^{-1}; eluent: methanol–water ($\varphi_r = 50 : 50$); flow-rate: 1 mL min^{-1}; UV detecting wavelength: 278 nm (Chen, 2010).

MCDA synthesis by Williamson reaction

Specific amounts of KI and methyl bromoacetate were first added to a three–neck flask containing anhydrous acetone (40 mL) under vigorous stirring. After 5 min, 4-methylcatechol (2.0 g, 16.12 mmol) and a specific amount of K_2CO_3 were added. The mixture was then heated at reflux using an oil bath, in which the synthesis reaction proceeded for 5 h under stirring and reflux. The mixture was subsequently filtered to remove any solids. After vacuum distillation of the acetone, 40 mL of a NaOH solution (pH = 8.5) was added to the liquid mixture to remove the unreacted 4-methylcatechol. Next, dichloromethane (CH_2Cl_2, 3 × 100 mL) was added to extract the product from the mixture. After drying over anhydrous Na_2SO_4 and vacuum distillation of the CH_2Cl_2, the crude product was further purified using column chromatography (eluent: ethyl acetate/cyclohexane ($\varphi_r = 1.5$)) (Drevermann et al., 2005; Qiao, 2009; Cui, 2008; Gaudin et al., 2007).

Synthesis of 7-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]dioxepine-2/4-carboxylic acid methyl ester via Dieckmann condensation reaction

Under a N_2 atmosphere and cooling using an ice/H_2O bath, a specific amount of KO^tBu was added to a flask containing a solution of the synthesised MCDA in anhydrous THF (45 mL). After 5 min, the flask was immersed in an oil bath at 70 ℃ for 30 min. Next, 200 mL ice/H_2O was poured into the flask and the pH of the mixture was adjusted to 2.5 by using HCl solution (36 mass %). After vacuum distilla-

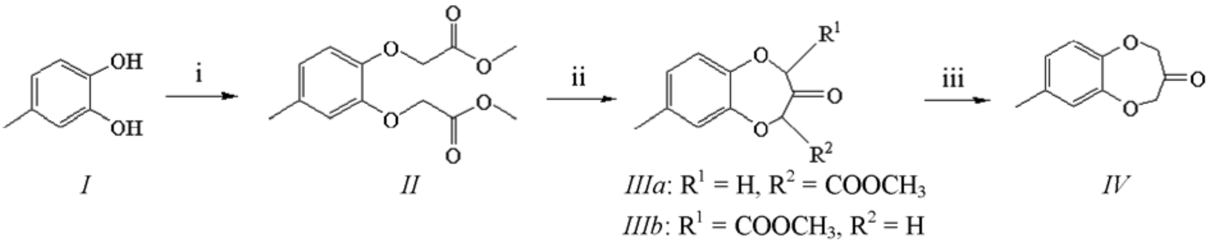

Fig. 1. Schematic diagram of synthesis of Calone 1951®. Reagents and conditions: (i) KI, methyl bromoacetate, K_2CO_3, anhydrous acetone; (ii) KO^tBu, anhydrous THF; (iii) anhydrous ethanol, 5 mass % HCl.

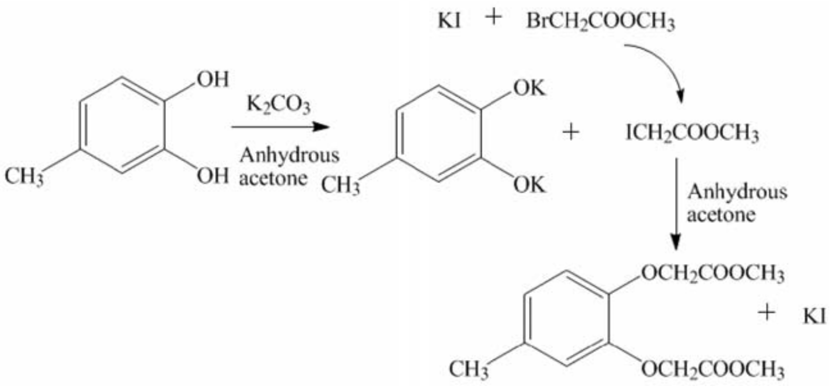

Fig. 2. MCDA synthesis via KI-catalysed Williamson reaction.

tion of THF, the reaction mixture was extracted using CH_2Cl_2 (3 × 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and the product was isolated by vacuum distillation (Drevermann et al., 2005; Qiao, 2009; Cui, 2008; Gaudin et al., 2007).

Synthesis of Calone 1951®

The product (approximately 3.7 g) from the Dieckmann reaction was transferred into a flask containing 45 mL of anhydrous ethanol and 45 mL of HCl (5 mass %). The flask was then immersed in an oil bath at 120 ℃ for 8 h. The reaction mixture was subsequently quenched with ice/H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). After drying over anhydrous Na_2SO_4, the crude Calone 1951® was isolated by vacuum distillation of the CH_2Cl_2, and purified using column chromatography (eluent: ethyl acetate/cyclohexane (φ_r = 1 : 2)) to obtain the final product (Drevermann et al., 2005; Qiao, 2009; Cui, 2008; Gaudin et al., 2007).

Results and discussion

Reaction mechanism

The synthesis of Calone 1951® via the successive Williamson reaction, Dieckmann condensation, and hydrolysis–decarboxylation reaction is illustrated in Fig. 1. In the Williamson reaction, the first intermediate MCDA (*II*) was synthesised from 4-methylcatechol (*I*) and methyl bromoacetate with KI as catalyst. In the Dieckmann condensation reaction, the second intermediates: 7-methyl-3-oxo-3,4-dihydro-2*H*- benzo[*b*][1,4]dioxepine-2/4-carboxylic acid methyl esters (*IIIa and IIIb*) were synthesised via intramolecular etherification under basic conditions. In the third reaction, Calone 1951® (*IV*) was synthesised by the hydrolysis and decarboxylation of intermediate *III* under acidic conditions.

The synthesis of *II* by the KI-catalysed Williamson reaction entailed three reactions (Fig. 2). First, phenoxide dianions were produced from *I* after the H^+ ions of its hydroxyl groups were removed with K_2CO_3 serving as a weak base. Meanwhile, methyl iodoacetate was generated from methyl bromoacetate by the nucleophilic substitution of bromine by iodine. Next, MCDA was synthesised by the reaction between the phenoxide dianions with methyl iodoacetate. Since methyl iodoacetate is more reactive than methyl bromoacetate, the addition of KI can significantly increase the product yield of *II*.

Product characterisation

MCDA

The melting point of the synthesised MCDA is measured as 49.3–49.8 ℃, in agreement with the literature value of 49–53 ℃ (Hügel et al., 2008; Pouchert, 1981).

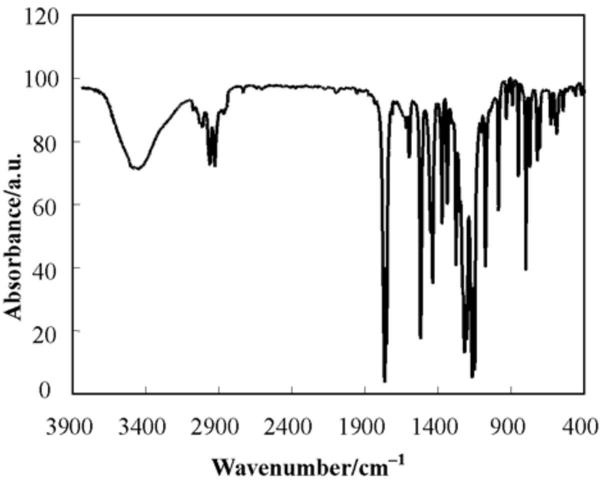

Fig. 3. IR spectrum of synthesised MCDA.

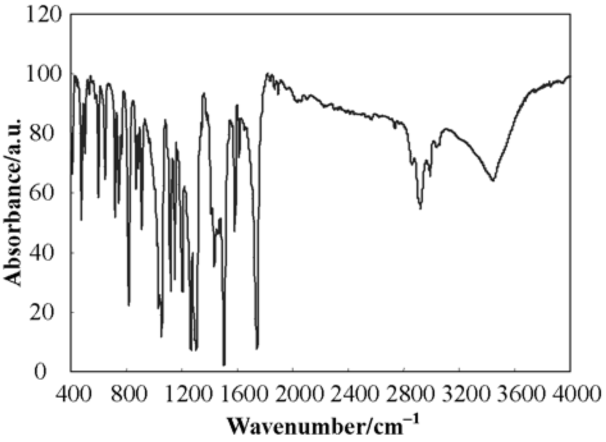

Fig. 4. IR spectrum of synthesised Calone 1951®.

HPLC analysis of the reaction mixture showed that the purity of the synthesised MCDA was approximately 99 %.

Fig. 3 shows the IR spectrum of the synthesised MCDA. The peaks at 2957.1 cm^{-1} and 2924.2 cm^{-1} are attributed to $-CH_3$ (asymmetric stretching vibration). The doublet peak at 1748.9–1762.5 cm^{-1} corresponds to the C═O group. The adsorption maxima at 1443.1 cm^{-1}, 1448.4 cm^{-1}, and 1517.6 cm^{-1} are all attributed to the C═C bonds of the benzene ring. The adsorption of $-CH_2-$ appears at 1369.7 cm^{-1} (bending vibration). The ether bond (C—O—C) is indicated by the peak at 1073.1 cm^{-1} (stretching vibration). The peaks at 795.8 cm^{-1} and 768.7 cm^{-1} are attributed to the C—H of the benzene ring.

In the ^{1}H NMR spectrum of the synthesised MDCA (Fig. S1), the two doublet peaks and one multiplet peak between $\delta = 6.80$ and $\delta = 6.69$ are attributed to the three hydrogen atoms of the benzene ring. The doublet peak between $\delta = 6.80$ and $\delta = 6.78$ is attributed to H_1, the other one at around $\delta = 6.69$ is attributed to H_2, and the multiplet peak between $\delta = 6.74$ and $\delta = 6.73$ is attributed to H_5. The two singlet peaks at $\delta = 4.70$ and $\delta = 4.69$ correspond to the $-CH_2-$ groups (H_{12}, H_7) of the two ester chains. The two peaks at $\delta = 3.79$ and $\delta = 3.78$ are attributed to the $-CH_3$ groups (H_{10}, H_9) of the ester chains, while the $-CH_3$ group (H_3) directly connected to the benzene ring is indicated by the peak at $\delta = 2.26$.

The ^{13}C NMR spectrum of MCDA is shown in Fig. S2, in which the peak at $\delta = 21.06$ is attributed to the carbon atom in the $-CH_3$ group (C_3) directly connected to the benzene ring. The two peaks at $\delta = 169.79$ and $\delta = 169.67$ correspond to the carbonyl carbon atoms of the two ester chains (C_{11} and C_8). The two adjacent peaks at $\delta = 52.30$ and $\delta = 52.26$ correspond to the two carbon atoms of the $-CH_3$ groups of the ester chains (C_{10}, C_9), while the $-CH_2$ groups (C_{12}, C_7) of the ester chains are indicated by the peaks at $\delta = 67.07$ and $\delta = 66.71$, respectively. The two peaks at $\delta = 147.90$ and $\delta = 145.90$ are due to the two carbon atoms of the benzene ring connected with the two ester chains (C_{13} and C_6). The C_4, C_1, C_5, and C_2 atoms of the benzene ring are demonstrated by the peaks at $\delta = 132.71$, $\delta = 123.00$, $\delta = 116.40$, and $\delta = 115.91$, respectively.

Calone 1951®

The melting point of Calone 1951® is determined as 38.1–40.7 ℃, which is in good agreement with the literature value (38–40 ℃; Pouchert (1981)).

The HPLC chromatogram of the Calone 1951® reaction mixture demonstrated the high purity of the product.

Fig. 4 shows the IR spectrum of the synthesised Calone 1951®. In the spectrum, the peak at 812.8 cm^{-1} is attributed to the C—H of the benzene ring. The adsorptions between 1053.1–1304.5 cm^{-1} correspond to the two ester bonds (C—O—C, stretching vibration). The C═C bonds of the benzene ring are indicated by the peak at 1505.6 cm^{-1}. The carbonyl group (C═O) of the ketone group is demonstrated by the strong adsorption at 1742.6 cm^{-1}. The stretching vibration of the $-CH_3$ appears at 2923.7 cm^{-1}.

The ^{1}H NMR and ^{13}C NMR spectra of the synthesised Calone 1951® are shown in Figs. S3 and S4, respectively. In Fig. S3, the two doublet peaks and one singlet peak between $\delta = 6.90$ and $\delta = 6.76$, the intensity ratio of which is close to 1 : 1 : 1, are attributed to the hydrogen atoms of the benzene ring. The doublet peak between $\delta = 6.90$ and $\delta = 6.88$ is attributed to H_1, the other doublet peak between $\delta = 6.78$ and $\delta = 6.81$ corresponds to H_2, and the singlet peak at $\delta = 6.81$ is attributed to the H_5. The $-CH_2-$ groups are indicated by the two single peaks at $\delta = 4.70$ (H_9) and $\delta = 4.68$ (H_7), while the $-CH_3$ group (H_3) is demonstrated by the adsorption at $\delta = 2.27$.

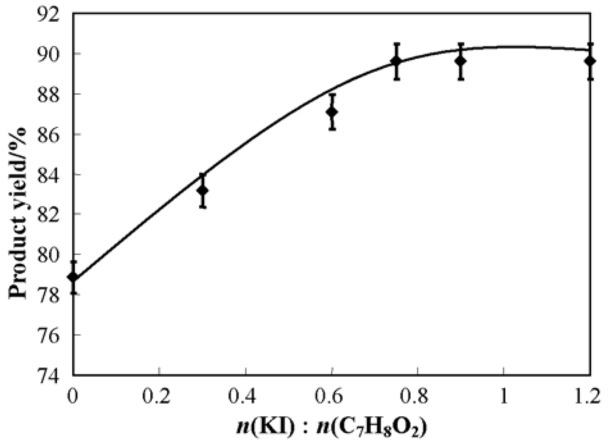

Fig. 5. Effect of amount of KI employed on MCDA yield. Operating conditions: $n(C_3H_5BrO_2) : n(C_7H_8O_2) = 3.5 : 1$; $n(K_2CO_3) : n(C_7H_8O_2) = 4 : 1$; reaction time = 5 h; reaction temperature = 70 °C; $m(C_7H_8O_2) = 2$ g; V(acetone) = 40 mL.

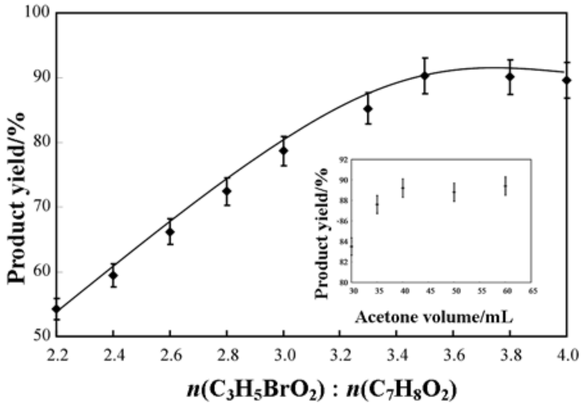

Fig. 6. Effect of methyl bromoacetate to 4-methylcatechol molar ratio on MCDA yield. Operating conditions: $n(\text{KI}) : n(C_7H_8O_2) = 0.75 : 1$; $n(K_2CO_3) : n(C_7H_8O_2) = 4 : 1$; reaction time = 5 h; reaction temperature = 70 ℃; $m(C_7H_8O_2) = 2$ g. The inset demonstrates the effect of solvent volume on MCDA yield.

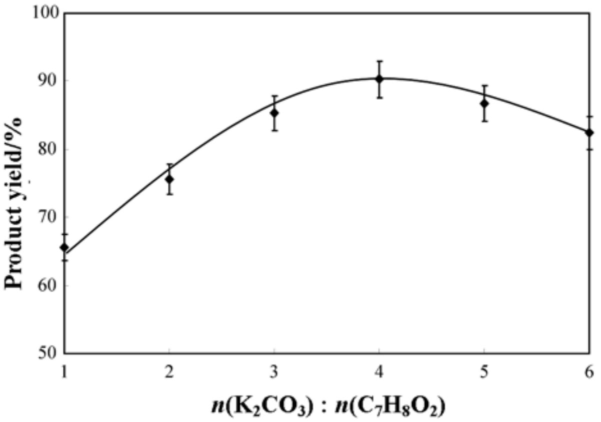

Fig. 7. Effect of K_2CO_3 on MCDA yield. Operating conditions: $n(\text{KI}) : n(C_7H_8O_2) = 0.75 : 1$; $n(C_3H_5BrO_2) : n(C_7H_8O_2) = 3.5 : 1$; reaction time = 5 h; reaction temperature = 70 ℃; $m(C_7H_8O_2) = 2$ g; V(acetone) = 40 mL.

In the ^{13}C NMR spectrum of the product (Fig. S4), the peak at $\delta = 20.67$ is attributed to the carbon atom in the –CH_3 group (C_3). The two peaks at $\delta = 75.60$ and $\delta = 75.93$ correspond to C_7 and C_9. C_2, C_5, and C_1 are indicated by the peaks at $\delta = 120.78$, $\delta = 121.31$, and $\delta = 124.46$, respectively. The C_4 peak appears at $\delta = 133.92$, the two adsorptions at $\delta = 146.21$ and $\delta = 148.08$ are attributed to C_6 and C_{10} of the benzene ring, respectively. The peak at $\delta = 204.96$ corresponds to the carbonyl carbon of the ketone group (C_8).

Operating conditions of Williamson reaction

In this section, the effect of the key operating factors on MCDA synthesis by the KI-catalysed Williamson reaction was first studied by single-factor experiments then a group of orthogonal experiments was employed to obtain the optimum operating conditions.

Fig. 5 demonstrates that the addition of KI can significantly increase the product yield of MCDA and the optimum value for the molar ratio between KI and 4-methylcatechol is 0.75. An increase in KI promotes the formation of methyl iodoacetate, which is beneficial to the synthesis of MCDA.

In the study by Miao et al. (2006) to synthesize isobutyl-5-nitro-2,4-dichlorophyl ether from 2,4-dichloro-nitrophenol, just 0.8 mass % KI of 2,4-dichloro-nitrophenol is sufficient to boost the reaction; while in the course of this reaction, a much larger amount of KI is required. This difference might be due to the distinction between the molecular structures of the two phenols, as 1,2-catechol is a diphenol. Moreover, the synthesis of isobutyl-5-nitro-2,4-dichlorophyl ether was implemented in a two-phase medium and a phase transfer catalyst was used, which can promote the catalytic efficiency of KI.

The product yield of MCDA was investigated at different molar ratios between methyl bromoacetate and 4-methylcatechol (I). Fig. 6 shows that the MCDA yield initially increases with an increase in the amount of methyl bromoacetate, attaining a plateau value when the molar ratio exceeds 3.5.

To clarify the volume effect (Fig. 6 inset), verification experiments with acetone with volume greater than 40 mL were employed, which demonstrated that the MCDA yield remained almost invariant with an increase in acetone volume and the solvent volume had a negligible effect on the MCDA yield.

Fig. 7 shows that the MCDA yield initially increases with an increase in the K_2CO_3 amount, at-

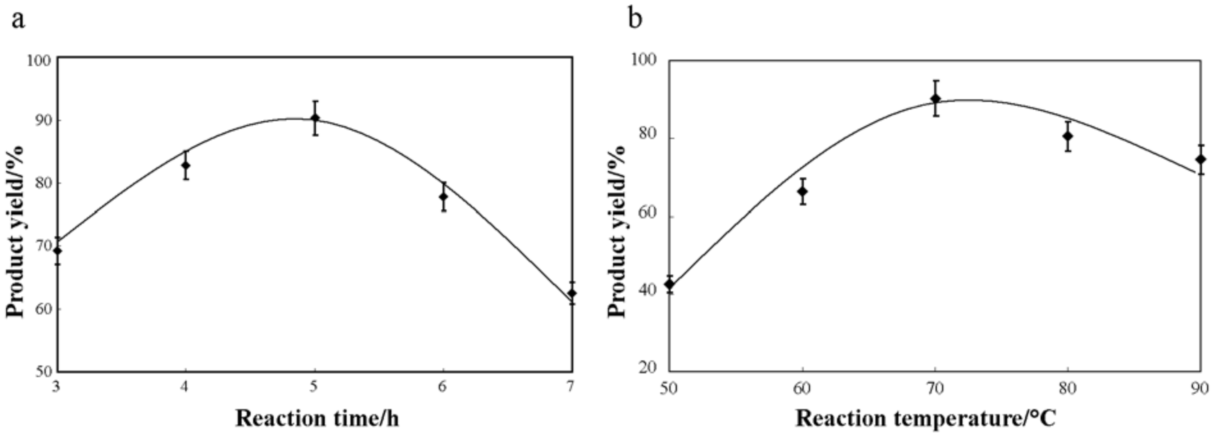

Fig. 8. Effect of reaction time (a) and temperature (b) on product yield. Operating conditions: $n(\mathrm{KI}) : n(\mathrm{C_7H_8O_2}) = 0.75 : 1$; $n(\mathrm{C_3H_5BrO_2}) : n(\mathrm{C_7H_8O_2}) = 3.5 : 1$; $n(\mathrm{K_2CO_3}) : n(\mathrm{C_7H_8O_2}) = 3.5 : 1$; $m(\mathrm{C_7H_8O_2}) = 2$ g; $V(\text{acetone}) = 40$ mL; a) reaction temperature = 70 ℃; b) reaction time = 5 h.

Table 1. Factors and levels of orthogonal experiments

Level	Factors				
	$n(\mathrm{KI}) : n(\mathrm{C_7H_8O_2})$	$n(\mathrm{C_3H_5BrO_2}) : n(\mathrm{C_7H_8O_2})$	$n(\mathrm{K_2CO_3}) : n(\mathrm{C_7H_8O_2})$	t/h	T/ ℃
I	0.6 : 1	3.2 : 1	3 : 1	4	60
II	0.75 : 1	3.5 : 1	4 : 1	5	70
III	0.9 : 1	3.8 : 1	5 : 1	6	80

taining its maximum when the molar ratio between $\mathrm{K_2CO_3}$ and 4-methylcatechol (I) is approximately 4.0. Subsequently, it decreases with a further increase in the $\mathrm{K_2CO_3}$ amount. In the Williamson reaction, $\mathrm{K_2CO_3}$ serves as an acid scavenger to facilitate the formation of phenolate di-anions and to provide a suitable pH environment. Excess $\mathrm{K_2CO_3}$ renders the basicity of the reaction system too high, resulting in a decrease in the product yield (Morrison et al., 1992).

Fig. 8 shows that the optimum time and temperature for the KI-catalysed Williamson reaction at 70 ℃ is 5 h. When the reaction temperature or time exceeds the optimum value, the enhancement of the side reactions leads to a decrease in the MCDA yield (Drevermann et al., 2005).

Orthogonal experiments

On the basis of the single factor experiments, a set of orthogonal experiments was employed to study the importance of the affecting factors and to obtain the optimum operating conditions. Since the interaction between KI and methyl bromoacetate is also important in addition to the five essential affecting factors, i.e. the KI amount, the molar ratio between methyl bromoacetate and 4-methylcatechol (I), the $\mathrm{K_2CO_3}$ amount, reaction temperature, and reaction time, a $\mathrm{L_{27}}$ (3^{13}) design (Fang & Ma, 2001) was selected. The affecting factors and corresponding values for the orthogonal experiments are listed in Table 1. The experimental design and results are shown in Table 2, where the range value (R) indicates the affecting degree of each affecting factor and K is the average product yield corresponding to each level of every affecting factor.

The range analysis shown in Table 2 demonstrates that the KI amount is the factor most affecting the product yield and its interaction with methyl bromoacetate is also significant, while the amount of methyl bromoacetate has a minor effect on the product yield. This result confirms the mechanism by which KI acts via reaction with methyl bromoacetate. The optimum operating conditions obtained from Table 2 are: $n(\mathrm{KI}) : n(\mathrm{C_7H_8O_2})$, 0.75 : 1; $n(\mathrm{C_3H_5BrO_2}) : n(\mathrm{C_7H_8O_2})$, 3.5 : 1; $n(\mathrm{K_2CO_3}) : n(\mathrm{C_7H_8O_2})$, 4.0 : 1; reaction time, 6 h; reaction temperature, 80 ℃. The verification experiments demonstrated that, under the optimum operating conditions, the MCDA yield can be as high as 95.4 %, the corresponding overall yield of Calone 1951® is up to 68 %, whereas the product yield of the Williamson reaction is only 78.5 % without the addition of KI (Cui, 2008).

Conclusions

In this paper, the synthesis of 4-methylcatechol dimethylacetate (MCDA) from 4-methylcatechol and methyl bromoacetate is investigated via the William-

Table 2. Results and analyses of orthogonal experiments

Exp.	$n(\text{KI}) : n(\text{C}_7\text{H}_8\text{O}_2)$	$n(\text{C}_3\text{H}_5\text{BrO}_2) : n(\text{C}_7\text{H}_8\text{O}_2)$	1×2	$n(\text{K}_2\text{CO}_3) : n(\text{C}_7\text{H}_8\text{O}_2)$	$\frac{t}{\text{h}}$	$\frac{T}{℃}$	$\frac{\text{Yield}}{\%}$
I	1	1	1	1	1	1	78.63
II	1	1	1	2	2	2	95.29
III	1	1	1	3	3	3	87.04
IV	1	2	2	1	2	3	86.09
V	1	2	2	2	3	1	92.59
VI	1	2	2	3	1	2	80.39
VII	1	3	3	1	3	2	81.27
VIII	1	3	3	2	1	3	92.91
IX	1	3	3	3	2	1	84.84
X	2	1	2	1	2	2	75.00
XI	2	1	2	2	3	3	90.15
XII	2	1	2	3	1	1	85.47
XIII	2	2	3	1	3	1	93.77
XIV	2	2	3	2	1	2	75.17
XV	2	2	3	3	2	3	91.91
XVI	2	3	1	1	1	3	94.91
XVII	2	3	1	2	2	1	90.69
XVIII	2	3	1	3	3	2	88.06
XIX	3	1	3	1	3	3	83.45
XX	3	1	3	2	1	1	85.95
XXI	3	1	3	3	2	2	77.27
XXII	3	2	1	1	1	2	76.10
XXIII	3	2	1	2	2	3	87.20
XXIV	3	2	1	3	3	1	89.13
XXV	3	3	2	1	2	1	68.86
XXVI	3	3	2	2	3	2	81.59
XXVII	3	3	2	3	1	3	71.57
K1	85.561	84.250	87.450	82.009	82.344	85.548	–
K2	87.237	85.817	81.301	87.949	84.128	81.127	–
K3	80.124	83.856	85.171	83.964	87.450	87.248	–
R	7.113	1.961	6.149	5.940	5.106	6.121	–

son reaction by adding KI as catalyst, which reacts with methyl bromoacetate to generate methyl iodoacetate. As methyl iodoacetate is more reactive, the MCDA yield was significantly increased. The structure and purity of the synthesised MCDA and Calone 1951® were first verified by melting point measurement, HPLC, IR, and NMR analyses. Next, the effect of the key operating factors on the Williamson reaction was investigated. The optimum operating conditions ($n(\text{KI}) : n(\text{C}_7\text{H}_8\text{O}_2) = 0.75 : 1$; $n(\text{C}_3\text{H}_5\text{BrO}_2) : n(\text{C}_7\text{H}_8\text{O}_2) = 3.5 : 1$; $n(\text{K}_2\text{CO}_3) : n(\text{C}_7\text{H}_8\text{O}_2) = 4.0 : 1$; reaction time = 6 h; reaction temperature = 80 ℃) were obtained via a group of orthogonal experiments. The verification experiments demonstrated that, under the optimum operating conditions, the MCDA yield can be increased from 78.5 % to 95.4 % by the addition of KI and the overall yield of Calone 1951® was up to 68 %.

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Supplementary data

Supplementary data associated with this article can be found in the online version of this paper (DOI: 10.2478/s11696-013-0359-z).

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