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Short communication

SHORT COMMUNICATION

Improved synthesis of quinocetone and its two deoxy metabolites

YUWEN LI, MEI QIU, YUBIN BAI, SHAOQI QU and ZHIHUI HAO*

Agricultural Bio-pharmaceutical Laboratory, Qingdao Agricultural University, Qingdao 266109, China and National-Local Joint Engineering Laboratory of Agricultural Bio-pharmaceutical Technology, Qingdao 266109, China

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Abstract: Oxidation of *o*-nitroaniline with sodium hypochlorite afforded benzofurazan oxide in 96 % yield, and treatment of benzofurazan oxide with acetylacetone in the presence of triethylamine gave 2-acetyl-3-methyl-quinoxaline-1,4-dioxide in 94 % yield. Finally, condensation of 2-acetyl-3-methyl-quinoxaline-1,4-dioxide with benzaldehyde using 4-(dimethylamino)pyridinium acetate as a catalyst led to quinocetone in 95 % yield. Subsequently, reduction of the synthesized quinocetone with sodium dithionite resulted in two deoxy derivatives, 1-(3-methyl-4-oxido-2-quinoxalinyl)-3-phenyl-2-propen-1-one and 1-(3-methyl-2-quinoxalinyl)-3-phenyl-2-propen-1-one in 88.5 and 92 % yield, respectively. Furthermore, the synthesized quinocetone, and its deoxy derivatives were characterized by ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

Keywords: quinocetone; deoxy quinocetone; 4-(dimethylamino)pyridinum acetate; dideoxy quinocetone; synthesis.

INTRODUCTION

Chemically known as 1-(3-methyl-1,4-dioxide-2-quinoxalinyl)-3-phenyl-2-propen-1-one, quinocetone (QCT, Scheme 1) is a quinoxaline-1,4-*N*-dioxide, the family members of which are bioactive compounds displaying antibacterial, antiviral, and antifungal activities.[1] QCT is widely used in veterinary medicine for swine, poultry, and aquatic animals due to its effectiveness and low toxicity. Two other family members, carbadox and olaquindox, were banned in 1999 due to their toxicity and food safety concerns.[2] In addition, QCT is currently applied as an antibacterial feed additive and as a growth promoter.[3] Thus, a facile and efficient synthesis of QCT would be agriculturally beneficial, particularly in livestock breeding and aquaculture industry.

* Corresponding author. E-mail: 81975048@qq.com
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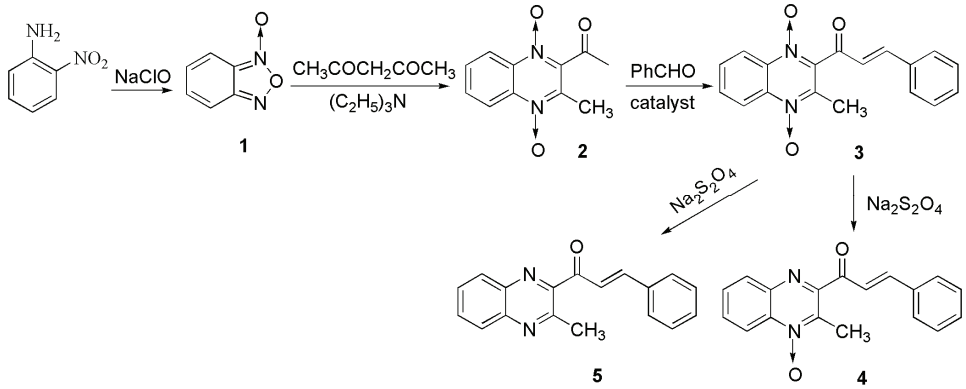
Currently, there are several methods for the synthesis of QCT, but all are challenged by low yields, use of toxic reagents and unrecyclable catalysts, leading to environmental concerns.[4,5]

Previous studies revealed that QCT is metabolized in the liver and kidneys of pigs and at least 31 metabolites were identified in pig urine,[6] including two deoxy metabolites **4** and **5** (Scheme 1). Research on the metabolites of a drug is beneficial to drug design and optimization, as well as guiding a reasonable clinical prescription, and hence, several syntheses of deoxy metabolites of quinocetone were developed.[7,8] However, these methods are tedious due to the use of different starting materials, and other toxic and corrosive reagents.

To obviate these drawbacks associated with the synthesis of quinocetone and its deoxy metabolites, an improved protocol for the chemical synthesis of quinocetone and its deoxy metabolites (Scheme 1) was developed in the present study.



Scheme 1. Improved synthesis of quinocetone and its two deoxy metabolites.

EXPERIMENTAL

Chemicals

4-*(*Dimethylamino)pyridinium acetate was synthesized according to a published procedure.[9] A sodium hypochlorite solution was freshly prepared prior to use according to a literature procedure.[10] Other chemicals of analytical reagent grade were purchased from commercial sources and used without further purification.

Apparatus

Melting points were determined on a digital melting point apparatus (WRS-1B) without correction. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solvent on a Bruker Avance III400 spectrometer, operating at 400 and 500 MHz for protons and 100 and 125 MHz for carbons. The chemical shift values are expressed in δ values relative to the internal standard tetramethylsilane. Elemental analysis was realised using an Elementar Vario EL III analyzer (Hanau, Germany).

*Synthesis of benzofurazan oxide (**1**)*

A mixture of sodium hydroxide (25 g, 0.625 mol) and water 100 mL was stirred until the solid had dissolved. The solution was cooled to 0 °C, and 50 g of crushed ice was added. The flask was then placed in an ice bath, and chlorine gas from a tank was bubbled through the solution until 0.29 mol chlorine had been absorbed. The solution of sodium hypochlorite was stored in the dark at 0 °C prior to use.

A mixture of potassium hydroxide (8.96 g, 0.160 mol) and 95 % ethanol (125 mL) was heated at 80 °C on an oil bath to obtain a clear alkali solution. To the warm alkali solution, *o*-nitroaniline (20.0 g, 0.145 mol) was added to obtain a deep red solution. The deep red solution was then cooled to 0 °C, and a freshly prepared sodium hypochlorite solution was added slowly under good stirring within 10 min. The flocculent yellow precipitate was collected by filtration on a Büchner funnel, and the cake was washed with 100 mL water and air-dried. Recrystallization of the crude product from 95 % ethanol gave benzofurazan oxide (**1**). Yield: 20.9 g (96 %); m.p.: 72.2–73.0 °C (lit:[10] 72–73 °C).

*Synthesis of 2-acetyl-3-methyl-quinoxaline 1,4-dioxide (**2**)*

A mixture of benzofurazan oxide **1** (10.2 g, 0.075 mol) and acetylacetone (12 g, 0.12 mol) in 25 mL ethanol was stirred at 45 °C, then triethylamine (4.55 g, 0.045 mol) was added to the solution and the mixture stirred for 2 h at 45 °C. On cooling, a yellow precipitate formed, which was collected by filtration, washed with 10 mL 95 % ethanol and air-dried. Recrystallization of the yellow precipitate from 95 % ethanol afforded compound **2**. Yield: 15.38 g (94 %); m.p.: 154.2–154.8 °C (lit:[4] 153–154 °C).

*Synthesis of 1-(3-methyl-1,4-dioxide-2-quinoxalinyl)-3-phenyl-2-propen-1-one (**3**)*

A mixture of 2-acetyl-3-methyl-quinoxaline 1,4-dioxide (**2**) (8.09 g, 0.040 mol) and benzaldehyde (6.37 g, 0.060 mol) in 50 mL ethanol was heated at 70 °C for 30 min to obtain a clear solution, and then 4-(dimethylamino)pyridinium acetate (0.364 g, 2.0 mmol), readily prepared according to literature,[9] was added to the solution. The solution was then stirred at 70 °C for 3 h. On cooling the solution to 0 °C, yellow crystals precipitated within 3 h. The yellow crystals were collected by filtration, washed with ethanol, and air-dried. The mother liquor was evaporated to recycle the catalyst 4-(dimethylamino)pyridinium acetate. Recrystallization of the yellow crystals afforded compound **3**. Yield: 12.3 g (95 %). Analytical and spectral data for **3** are presented in the Supplementary material to this paper.

*Synthesis of 1-(3-methyl-4-oxido-2-quinoxalinyl)-3-phenyl-2-propen-1-one (**4**)*

Sodium dithionite (90 %, 12 mmol) was added portionwise to a mixture of 1-(3-methyl-1,4-dioxide-2-quinoxalinyl)-3-phenyl-2-propen-1-one (**3**, 2.90 g, 10 mmol) in 50 mL 95 % ethanol under good stirring. The mixture was stirred under reflux for 3 h and then cooled in an ice-bath, whereby a yellow precipitate formed. The yellow precipitate was washed with water and air-dried to give 2.57 g yellow crystal of **4**. Yield: 88.5 %. Analytical and spectral data for **4** are presented in the Supplementary material to this paper.

*Synthesis of 1-(3-methyl-2-quinoxalinyl)-3-phenyl-2-propen-1-one (**5**)*

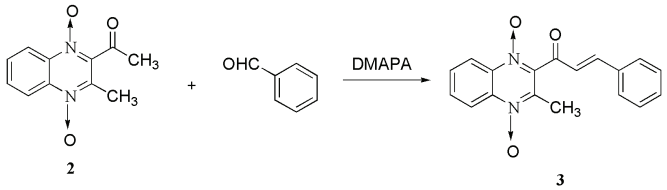
90 % sodium dithionite (30 mmol) was added portionwise to a mixture of 1-(3-methyl-1,4-dioxide-2-quinoxalinyl)-3-phenyl-2-propen-1-one (**3**, 3.48 g, 12 mmol) in 120 mL 95 % ethanol with good stirring. The mixture was stirred under reflux for 4 h and then cooled in an ice-bath, and yellow precipitate produced. The yellow precipitate was washed with water, and air-dried to give 3.02 g yellow crystal **5**. Yield: 92 %. Analytical and spectral data of **5** were presented in Supplementary material to this paper.

RESULTS AND DISCUSSION

As shown in Scheme 1, benzofurazan oxide **1** was readily synthesized in 96 % yield as reported in the literature.[10] According to a previous synthesis of intermediate **2**,[4] reaction of intermediate **1** with acetylacetone in the presence of triethylamine generated intermediate **2** in 94 % yield. Conventionally, condensation of intermediate **2** with benzaldehyde using different catalysts produced quinocetone (**3**) in various yields, ranging from 65.2 to 83 %. Both diethylamine[4] and sodium carbonate[5] are conventional catalysts in the synthesis of quinocetone (**3**) by reaction of intermediate **2** with benzaldehyde. However, these catalysts are difficult to recycle and are detrimental to the environment, especially for large--scale preparations.

4-(Dimethylamino)pyridinium acetate (DMAPA) was initially developed by Nowrouzi, Farahi and Irajzadeh[9] to catalyze synthesis of 5-substituted-1*H*-tetrazoles through reaction of nitriles with sodium azide. For the first time, we applied 4-(dimethylamino)pyridinium acetate as a recyclable catalyst to synthesize quinocetone (**3**) by reaction of intermediate **2** with benzaldehyde. Details for the screening of the dosage of catalyst DMAPA are summarized in Table I.

TABLE I. Optimization of the dosage of catalyst DMAPA



2 **3**

Entry	Mole ratio[a]	DMAPA[b] / mol %	Temperature, °C	Time, h	Yield, %
1	1:1.5	1	70	3	79.2
2	1:1.5	3	70	3	86.4
3	1:1.5	5	70	3	95.1
4	1:1.5	7	70	3	94.9
5	1:1.5	9	70	3	94.8

[a]Mole ratio of compound **2** to benzaldehyde; [b]content of compound **2**

The data in Table I revealed that the optimal dosage of DMAPA was 5 mol % of compound **2.** In terms of the yield of quinocetone (**3**), DMAPA catalyst is superior to the existing catalysts for the synthesis of quinocetone**.** Moreover, this catalyst is recyclable, making the procedure for synthesis of **3** environmentally-friendly and commercially-viable.

Reduction of quinocetone (**3**) with sodium dithionite yielded compounds **4** and **5** by altering the mole ratio of sodium dithionite to quinocetone. Experiments showed that a mole ratio of sodium dithionite to quinocetone (**3**) of 1.2:1 generated deoxy metabolite **4** in 88.5 % yield. However, further increasing the mole

ratio of sodium dithionite to quinocetone (**3**) decreased the yield of **4**, while increasing the yield of dideoxy quinocetone **5**. When the mole ratio of sodium dithionite to **3** was set at 3:1, the dideoxy quinocetone **5** was acquired in 92 % yield.

CONCLUSIONS

In summary, an improved and practical protocol for the synthesis of quinocetone (**3**) in three sequential chemical steps was developed in 85.7 % total yield, which was superior to the existing protocol for the synthesis of quinocetone. Moreover, deoxyquinocetone 4 and dideoxyquinocetone 5 were conveniently synthesized in 88.5 and 92 % yield, respectively, by reduction of the synthesized quinocetone **3** with sodium dithionite. In addition to the higher yields of quinocetone (**3**), deoxy quinocetone **4** and dideoxy quinocetone **5**, this protocol has the advantages of operational simplicity, chromatography-free separation and purification by recrystallization throughout the whole procedure and the recyclability of the 4-(dimethylamino)pyridinium acetate catalyst.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of the journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

УНАПРЕЂЕНА СИНТЕЗА ХИНОЦЕТОНА И ЊЕГОВА ДВА ДЕОКСИ МЕТАБОЛИТА

YUWEN LI, MEI QIU, YUBIN BAI, SHAOQI QU и ZHIHUI HAO

Agricultural Bio-pharmaceutical Laboratory, Qingdao Agricultural University, Qingdao 266109, China и National-Local Joint Engineering Laboratory of Agricultural Bio-pharmaceutical Technology, Qingdao 266109, China

Оксидацијом *о*-нитроанилина натријум-хипохлоритом добијен је у приносу од 96 % бензофуразан-оксид, који у реакцији са ацетилацетоном, у присуству триетиламина, даје 2-ацетил-3-метил-хиноксалин-1,4-диоксид у приносу од 94 %. У наредном реакционом кораку, у реакцији кондензације 2-ацетил-3-метил-хиноксалин-1,4-диоксида и бензалдехида, у присуству 4-(диметиламино)пиридинијум-ацетата као катализатора, добијен је хиноцетон у приносу од 95 %. Реакцијом редукције у наредном реакционом кораку, употребом натријум-дитионита, добијени су деокси деривати 1-(3-метил-4-оксидо-2-хиноксалинил)-3-фенил-2-пропен-1-он и 1-(3-метил-4-оксидо-2-хиноксалинил)-3-фенил-2-пропен-1-он у приносима 88,5 и 93 %, редом. Синтетисана једињења, хиноцетон и његови деокси деривати, окарактерисани су ^{1}H-NMR и ^{13}C-NMR спектроскопијом и елементалном анализом.

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