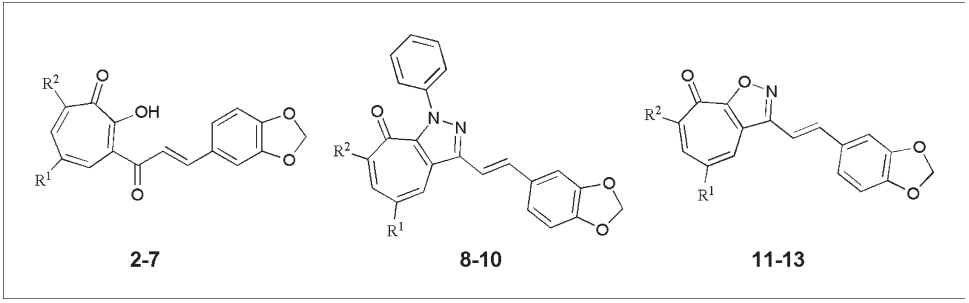
Synthesis and Characterization of Bromo-, Arylazo-, and Heterocyclic-Fused Troponoids Containing a 1,3-Benzodioxole System

Yang Li, Mingchun Sun, and Wentao Gao*

Institute of Superfine Chemicals, Bohai University, Jinzhou, 121000 China
*E-mail: isfcwentao@163.com

Received May 11, 2010
DOI 10.1002/jhet.702
Published online 21 October 2011 in Wiley Online Library (wileyonlinelibrary.com).



A facile synthesis of a series of novel bromo-, arylazo-, and heterocyclic fused troponoid compounds containing 1,3-benzodioxole system is described. The 7-bromo-, 5,7-dibromo-, and 5-arylazo-substituted 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]tropolones (**2**, **3**, and **5**–**7**) were obtained by direct bromination or azo-coupling reactions of 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop- 2-enoyl]tropolone (**1**) with bromine, and diazonium salts of aniline derivatives, respectively. 3-[(2*E*)-3-(1,3-Benzodioxol-5-yl)prop-2-enoyl]-5-bromotropolone (**4**) was obtained from 3-acetyl-5-bromotropolone *via* one-pot aldol dehydration reaction with piperonal. Tropolones **2, 3**, and **4** were subjected to nucleophilic cyclization with bifunctional hydroxylamine hydrochloride and phenylhydrazine hydrochloride to give the corresponding isoxazolo- and pyrazolo-fused tropones (**8**–**13**), respectively.

J. Heterocyclic Chem., **49**, 167 (2012).

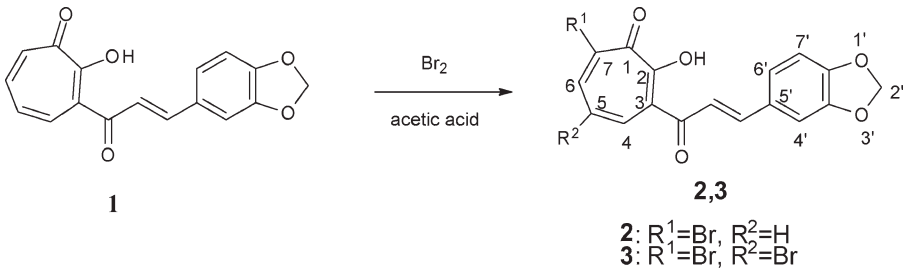
INTRODUCTION

Since 1945, when Dewar correctly predicted that natural products such as colchicine and derivatives of puberulonic acid encompass the troponoid ring [1], the importance of troponoid and its heterocyclic-fused derivatives has been well recognized and considerable efforts have been devoted aiming at understanding and exploiting the chemistry of the cyclohepta-2,4,6-trienone (tropone) [2]. Some natural products containing a tropolone nucleus or bicyclic heterocyclic-fused tropone moiety exhibit potent biological and pharmacological activities such as antitumour and antimalarial activities [3]. There are several reports dealing with the preparation of troponoid derivatives and their corresponding biological evaluations [4]. In this regard, the works carried by Yamato *et al*. [5] and Crozet and coworkers [6] are of special interest. In addition, the tropolone moiety plays an important role in molecular assemblies for a faster and efficient lead generation towards the new drug discovery. But tropolone derivatives are scarce in nature [7], occurring only in lower plants and fungi [8], and limited information is available on these compounds. Therefore, synthesis of troponoid compounds continues to be a considerable synthetic challenge.

On the other hand, 1,3-benzodioxoles, one of the major subclasses of many natural products such as safrole [9], Leucettamine B [10], Steganacin [11], and egonol [12], exhibit a wide variety of biological activities [13–17], such as cytotoxic activity against several human tumor cell lines including human colon carcinoma cells [18] and multidrug-resistant nasopharyngeal carcinoma cells [19]. The 1,3-benzodioxole framework can be identified in the clinical antitumour agents etoposide, teniposide [20], and lignan lactone podophylotoxin [21] and the structure–activity relationships showed that the 1,3-benzodioxole moiety is fundamental for the cytotoxic activity because it can be metabolized by CYP to form metallo-carbene intermediates which could be responsible for the antitumor activity of lignans [22,23]. In addition, the presence of 1,3-benzodioxole moiety in some other bioactive molecules drastically alters their pharmacological properties. For example, among the many compounds isolated, the 1,3-benzodioxole-bearing coumarins show antiplatelet aggregation activity [24].

In light of these findings and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and efficient lead

Scheme 1. Synthesis of 7-bromo- and 5,7-dibromo-substituted tropolones **2,3**.



1 **2,3**

2: R^1=Br, R^2=H
3: R^1=Br, R^2=Br

generation toward the new drug discovery [25], we wish to report herein the synthesis of novel 1,3-benzodioxole-bearing tropolone as well as heterocyclic-fused tropone derivatives.

RESULTS AND DISCUSSION

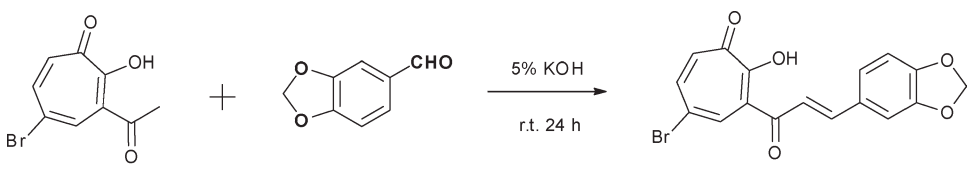
As far as we know, 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-tropolone (**1**) has been synthesized conveniently for many years [26a]. However, further modification of it is very limited [26b], despite its important potential biological activities. In this regard we previously reported the synthesis of isoxazolo- and pyrazolo-fused tropones containing 1,3-benzodioxole system [27]. However, the report is of episodic character and no efforts have been made to develop a general synthesis of this type of compounds. Thus, we are very interested in transforming compound **1** into various interesting 1,3-benzodioxole-bearing troponoid derivatives, which should be useful precursors for the synthesis of new biologically active tropolone derivatives.

We first carried out the bromination reaction of **1** with bromine as shown in Scheme 1. When treated with an equimolar amount of bromine in acetic acid in the presence of sodium acetate, 7-bromo-substituted tropolone **2** was obtained in 72% yields. Under the same reaction conditions the bromination reaction with two equivalents of bromine gave 5,7-dibromotropolone **3** in 67% yield.

The structures of **2** and **3** were established based on spectral data. In the ^{1}H NMR spectra of compounds **2**, **3**, the signals for the two vinyl protons and the five 1,3-benzodioxol protons were observed and their spectral pattern is very similar to that of the starting compound **1**, indicating that the bromination reaction occurred selectively on the tropolone ring. In the ^{1}H NMR spectrum of **2**, the signals from two hydrogens of C_4 and C_6 appeared as two doublet signals at 7.74 (d, 1H, J = 11.0 Hz) and 8.26 (d, 1H, J = 11.0 Hz), which arose a result of coupling with the C_5 hydrogen. The signal corresponding to the C_5 hydrogen appears as a doublet of doublets at 7.27 ppm (dd, 1H, J = 11.0, 10.8 Hz), which arose from coupling with both the C_4 and C_6 hydrogen atoms. These observations clearly indicated the formation of a 7-bromo-substituted product **2**. The molecular formula was established to be $C_{17}H_{11}BrO_5$ by its HRMS spectrum, which shows a *pseudo*-molecular-ion peak at *m*/*z* 396.9686 ($[M+Na]^+$; calc. for $C_{17}H_{11}^{79}BrNaO_5^+$: 396.9682), indicating the presence of twelve degrees of unsaturation. Similarly, the structure of **3** was fully characterized using ^{1}H NMR and HRMS spectra. The main feature of its ^{1}H NMR spectrum shows two doublet signals at 7.82 and 8.49 ppm with a coupling constant J = 1.95 Hz, which is a typical value (1–3 Hz) for *meta*-protons coupling in tropolone ring. The molecular formula of compound **3** was deduced to be $C_{17}H_{10}Br_2O_5$ from its HRMS, which shows a *pseudo*-molecular-ion peak at *m*/*z* 474.8781 ($[M+Na]^+$; calc. for $C_{17}H_{10}^{79}Br_2NaO_5^+$: 474.8785), indicating the presence of 12° of unsaturation. These observations supported that two bromine atoms were substituted at the 5- and 7-positions of the tropolone ring.

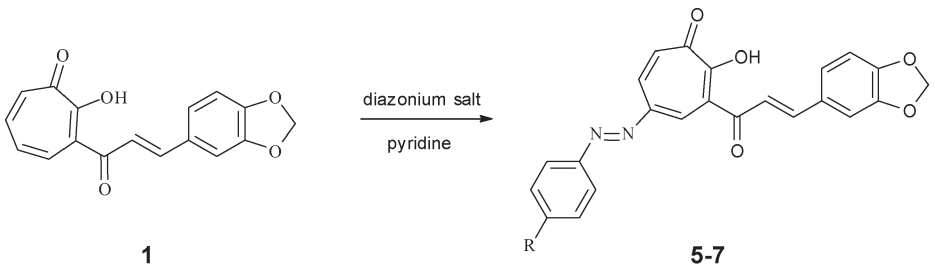
However, 5-bromo-substituted tropolone **4** could not obtained by direct bromination from compound **1** using bromine because of the occurrence of bromination on 7-position. Thus, we selected 3-acetyl-5-bromotropolone (**1′**) as a starting compound to react with 1.5 equimolar

Scheme 2. Synthesis of the desired 5-bromo-substituted tropolone **4**.



1' **2'** **4**

Scheme 3. Synthesis of 5-arylazo-substituted target compounds **5**–**7**.



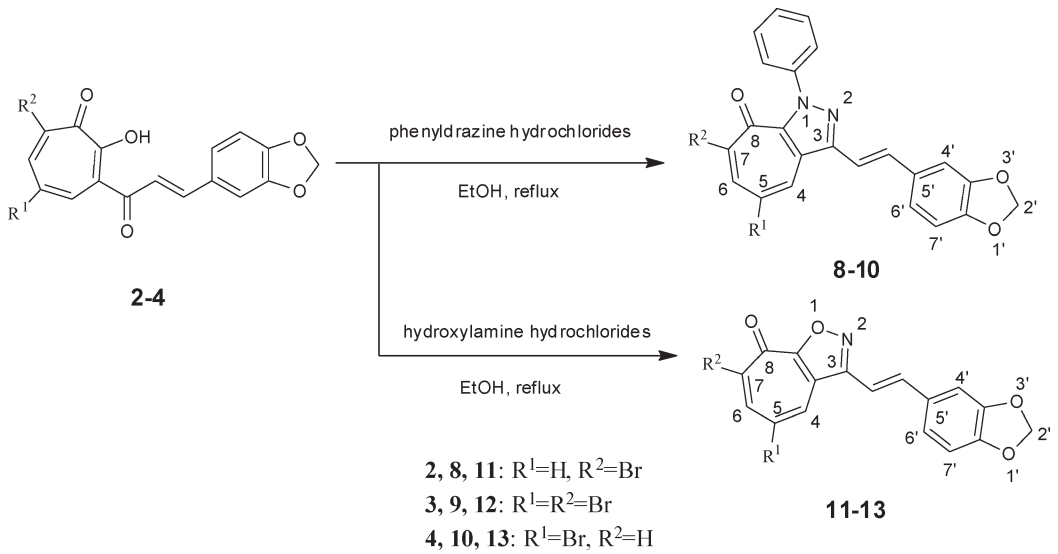
5: R= H; **6**: R=Me; **7**: R=NO_2

piperonal (**2′**) to give the desired 5-bromo product **4** in 89% yield *via* one-pot aldol dehydration reaction in 50% aq. methanol in the presence of 5% aq. KOH. The synthetic route was shown in Scheme 2.

The spectral data of **4** are in accordance with the assumed structure. Its ^{1}H NMR spectrum exhibited a singlet at 6.01 (2H), a doublet at 6.81 (1H, J = 1.6 Hz), a doublet at 6.93 (1H, J = 7.9 Hz), and a doublet of doublets at 7.05 (1H, J = 7.9, 1.6 Hz), two doublets centered at 7.08 and 7.62 with a coupling constant 15.9 Hz, representing the side-chain seven protons of (3-benzo[1,3]dioxol-5-yl)acryloyl moiety. The splitting pattern of the tropolone protons showed a doublet at 8.18, a doublet at 7.71, and a doublet of doublets at 7.43.

It is well known that arylazo compounds, which have been widely utilized over the years in various fields such as dyes [28], biomedicine [29], and organic synthesis [30], have recently found advanced potential applications as photosensitive species in photographic or electrophotographic systems and are the dominant organic photoconductive materials in commercial copiers [31]. Thus, we are interested in the synthesis of arylazo-substituted 1,3-benzodioxol-bearing tropolones. The synthesis of so far unreported 5-aryldiazenyl-substituted tropolones was shown in Scheme 3. The azo-coupling reactions of 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-tropolone (**1**) with diazonium salts of aniline derivatives in pyridine took place selectively at the 5-position of the tropolone ring to give the corresponding arylazo derivatives **5**–**7** in the yields of 63%, 72%, 52%, respectively. The resulting products of the reactions were easily identifiable by proton NMR. For example, in the ^{1}H NMR spectrum of compound **6**, the characteristic chemical shifts of the three protons attached to the tropolone ring were found at 7.55 ppm as a doublet (J = 11.2 Hz) for C_7 proton, at 8.26 ppm as a doublet of doublets (J = 11.3, 2.1 Hz) because of C_6 proton, and at 8.45 ppm as a doublet (J = 2.10 Hz) assignable to C_4 proton. The splitting pattern is very similar to that of the 5-brom tropolone **1**. The four protons of *p*-tolylazo moiety resonated as two doublets at 7.31 (2H, d, J = 8.2 Hz) and 7.82 ppm (2H, d, J = 8.2 Hz).

Scheme 4. Synthesis pyrazolo- and isoxazolo-fused target compounds **8**–**13**.



2, 8, 11: R^1=H, R^2=Br
3, 9, 12: R^1=R^2=Br
4, 10, 13: R^1=Br, R^2=H

Recently, we have reported the synthesis of some new heterocyclic-fused tropone compounds such as cyclohepta[*b*]pyran-4,9-diones [32]. In continuation of our studies on the synthesis of novel and interesting heterocyclic tropone derivatives, we herein synthesized six novel isoxazolo- and pyrazolo-fused tropones **8–13** by refluxing compounds **2**, **3**, or **4** with hydroxylamine hydrochloride or phenylhydrazine hydrochloride in EtOH as shown in Scheme 4. Completion of the reactions was monitored by thin layer chromatography (TLC).

The structures of all these newly synthesized tropones were established based on spectral data. The main features of the ^{1}H NMR data of compounds **8–13** showed the absence of the signal at δ 9.69–9.74 belonging to OH moiety of the precursor. Their IR spectra were also devoid of the stretching vibration bands resembling the OH moiety of the precursor, and exhibited only one typical carbonyl absorption for the tropone ring at 1624–1656 cm^{-1}. Further, the structures assigned for these reaction products were fully supported by their HRMS, which established their molecular formulas in accordance with their suggested molecular structures. In addition, all the compounds **8–13** had the negative coloring test with iron(III) chloride in methanol solution.

In summary, the synthesis of a series of hitherto unreported bromo-, arylazo-, and heterocyclic-fused troponoids containing 1,3-benzodioxol system has been achieved. The novel synthesized compounds should allow us, in the future, to investigate structure-activity relationships over various biotests. In addition, the products represent potentially useful synthetic building blocks in medicinal chemistry.

EXPERIMENTAL

General. All chemicals (**AR** graded) were commercially available and used without further purification. Melting points (uncorrected) were determined by using **WRS-1B** melting points apparatus. ^{1}H NMR was measured with a BRUKER BRX 600 at 400 or 500 MHz. The reported chemical shifts were against TMS. Mass spectra were recorded on a Micromass Platform liquid chromatography mass spectrometry-electrospray ionization. HRMS (ESI) data were acquired on a Bruker Customer micrOTOF-Q 125 high-resolution mass spectrometer with ESI. The progress of the reactions was monitored by TLC on silica gel **GF254** using ethyl acetate as eluent.

Synthesis of 3-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-7-bromotropolone (2). To a stirred solution of 3-[(2*E*)-3-(1, 3-benzodioxol-5-yl)prop-2-enoyl]-tropolone (**1**) (0.296 g, 1 mmol) and sodium acetate (0.125 g) in acetic acid (50 mL) was added dropwise a solution of bromine (0.160 g, 1 mmol) in acetic acid (2 mL) at room temperature. After stirring for 2 h, water (100 mL) was added. The precipitate was collected and recrystallized from ethyl acetate. Yield 62%; mp: 171–172°C. IR (KBr, ν, cm^{-1}): 3421 (OH), 1654 (C=O), 1610 (C=O); ^{1}H NMR (dimethyl sulfoxide [DMSO]-d_6, 500 MHz) (δ, ppm): 6.04 (s, 2H, OCH_2O), 6.85 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 6.99 (d, 1H, J = 7.9 Hz, 1,3-benzodioxol H-7′), 7.06 (dd, 1H, J = 7.9, 1.6 Hz, 1,3-benzodioxol H-6′), 7.13 (d, 1H, J = 15.9 Hz, =CH), 7.27 (dd, 1H, J = 11.0, 11.0 Hz, tropolone H-5), 7.62 (d, 1H, J = 15.9 Hz, =CH), 7.74 (d, 1H, J = 11.0 Hz, tropone H-6), 8.26 (d, 1H, J = 11.0 Hz, tropolone H-4), 9.78 (s, 1H, OH). ESI-HRMS calc. for $C_{17}H_{11}^{79}BrNaO_5^+$ $[M+Na]^+$: 396.9682; found: 396.9686.

Synthesis of 3-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-5,7-dibromotropolone (3). To a stirred solution of 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-tropolone (**1**) (0.296 g, 1 mmol) and sodium acetate in acetic acid (50 mL) was added dropwise a solution of bromine (0.320 g, 2 mmol) in acetic acid (2 mL) at room temperature. After stirring for 2 h, water (100 mL) was added. The precipitate was collected and recrystallized from ethyl acetate. Yield 67%; mp: 179–180°C. IR (KBr, ν, cm^{-1}): 3433 (OH), 1651 (C=O), 1607 (C=O); ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm): 6.02 (s, 2H, OCH_2O), 6.82 (d, 1H, J = 7.9 Hz, 1,3-benzodioxol H-7′), 6.96 (d, 1H, J = 15.85 Hz, =CH), 7.06 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 7.08 (dd, 1H, J = 7.9, 1.6 Hz, 1,3-benzodioxol H-6′), 7.53 (d, 1H, J = 15.85 Hz, =CH), 7.82 (d, 1H, J = 1.95 Hz, tropolone H-6), 8.49 (d, 1H, J = 1.95 Hz, tropolone H-4), 9.74 (s, 1H, OH). ESI-HRMS calc. for $C_{17}H_{10}^{79}Br_2NaO_5^+$ $[M+Na]^+$: 474.8785; found: 474.8781.

Synthesis of 3-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-5-bromotropolone (4). To a stirred solution of 3-acetylt-5-bromotropolone (0.60 g, 2.4 mmols) and piperonal (0.225 g,1.5 mmol) was added dropwise an aqueous solution of 5% KOH (12 mL). The resulting reaction mixture was stirred at room temperature for 24 h followed by acidification with 1 M HCl. The resulting precipitate was collected by filtration, washed with water, dried, and recrystallized from methanol to give product **4** in 89% yield; mp: 207–208°C. IR (KBr, ν, cm^{-1}): 3443 (OH), 1663 (C=O), 1597 (C=O); ^{1}H NMR (DMSO-d_6, 500 MHz) (δ, ppm): 6.02 (s, 2H, OCH_2O), 6.81 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 6.93 (d, 1H, J = 7.9 Hz, 1,3-benzodioxol H-7′), 7.05 (dd, 1H, J = 7.9, 1.6 Hz, 1,3-benzodioxol H-6′), 7.08 (d, 1H, J = 15.9 Hz, =CH), 7.43 (dd, 1H, J = 11.2, 2.0 Hz, tropolone H-6), 7.62 (d, 1H, J = 15.9 Hz, =CH), 7.71 (d, 1H, J = 11.1 Hz, tropolone H-7), 8.18 (d, 1H, J = 1.9 Hz, tropolone H-4), 9.83 (s, 1H, OH). ESI-HRMS calc. for $C_{17}H_{11}^{79}BrNaO_5^+$ $[M+Na]^+$: 396.9682; found: 396.9691.

General procedure for the azo-coupling reaction of 3-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-tropolone (1) with diazonium salts of anilines. To an ice-cooled stirred solution of compound **1** (0.296 g, 1 mmol) in pyridine (4 mL), was added dropwise arenediazonium chloride solution (2 mL), prepared from anilines (2.0 mmols) and $NaNO_2$ (0.139 g, 2.0 mmol). After additional stirring for 3 h, the precipitate was collected and recrystallized from benzene or ethyl acetate to give 3-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]-5-arylazotropolones **5–7**.

3-[(2E)-3-(1,3-Benzodioxol-5-yl)prop-2-enoyl]-5-phenyldiazenyltropolone (5). Yield 63%; mp: 191–192°C. IR (KBr, ν, cm^{-1}): 3238 (OH), 1651(C=O), 1602 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 6.01 (s, 2H, OCH_2O), 6.82 (d, 1H, J = 8.2 Hz, 1,3-benzodioxol H-7′), 7.09 (d, 1H, J = 15.8 Hz, =CH), 7.13 (dd, 1H, J = 8.1, 1.6 Hz, 1,3-benzodioxol H-

6′), 7.16 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 7.35–7.51 (m, 5H, ArH), 7.58 (d, 1H, J = 11.2 Hz, tropolone H-7), 7.62 (d, 1H, J = 15.8 Hz, =CH), 8.21 (dd, 1H, J = 11.0, 2.1 Hz, tropolone H-6), 8.33 (d, 1H, J = 2.10 Hz, tropolone H-4), 9.50 (s, 1H, OH). ESI-HRMS calc. for $C_{23}H_{16}N_2NaO_5^+$ $[M+Na]^+$: 423.0951; found: 423.0955.

3-[(2E)-3-(1,3-Benzodioxol-5-yl)prop-2-enoyl]-5-p-tolylazotropolone (6). Yield 72%; mp: 193–195°C. IR (KBr, ν, cm^{-1}): 3307 (OH), 1644(C=O), 1609 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 2.44 (s, 3H, CH3), 6.01 (s, 2H, OCH_2O), 6.81 (d, 1H, J = 8.1 Hz, 1,3-benzodioxol H-7′), 7.06 (d, 1H, J = 15.8 Hz, =CH), 7.08 (dd, 1H, J = 8.1, 1.6 Hz, 1,3-benzodioxol H-6′), 7.11 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 7.31 (d, 2H, J = 8.2 Hz, benzene-H), 7.55 (d, 1H, J = 11.2 Hz, tropolone H-7), 7.58 (d, 1H, J = 15.8 Hz, =CH), 7.82 (d, 2H, J = 8.3 Hz, benzene-H), 8.26 (dd, 1H, J = 11.3, 2.1 Hz, tropolone H-6), 8.45 (d, 1H, J = 2.10 Hz, tropolone H-4), 9.58 (s, 1H, OH). ESI-HRMS calc. for $C_{24}H_{18}N_2NaO_5^+$ $[M+Na]^+$: 437.1109; found: 437.1114.

3-[(2E)-3-(1,3-Benzodioxol-5-yl)prop-2-enoyl]-5-(4-nitrophenyl)diazenyltropolone (7). Yield 52%; mp: 292–294°C. IR (KBr, ν, cm^{-1}): 3320 (OH), 1649 (C=O), 1611 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 6.04 (s, 2H, OCH_2O), 6.85 (d, 1H, J = 8.1 Hz, 1,3-benzodioxol H-7′), 7.12 (d, 1H, J = 15.8 Hz, =CH), 7.17 (dd, 1H, J = 8.1, 1.6 Hz, 1,3-benzodioxol H-6′), 7.22 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 7.43 (d, 2H, J = 8.4 Hz, benzene-H), 7.62 (d, 1H, J = 15.8 Hz, =CH), 7.65 (d, 1H, J = 11.2 Hz, tropolone H-7), 7.88 (d, 2H, J = 8.3 Hz, benzene-H), 8.34 (dd, 1H, J = 11.3, 2.1 Hz, tropolone H-6), 8.55 (d, 1H, J = 2.10 Hz, tropolone H-4), 9.95 (s, 1H, OH). ESI-HRMS calc. for $C_{23}H_{15}N_3NaO_7^+$ $[M+Na]^+$: 468.0802; found: 468.0785.

General procedure for the preparation of 3-[(E)-2-(1,3-benzodioxol-5-yl)vinyl]-1-phenylcyclohepta[c]pyrazol-8(1H)-ones (8–10). A mixture of compound **2**, **3,** or **4** (1 mmol) and phenyldrazine hydrochloride (2.0 mmols) in ethanol (10 mL) was refluxed for 24 h. After the reaction was over as monitored by TLC, the precipitate was collected and recrystallized from ethyl acetate to give products **8–10**.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-7-bromo-1-phenylcyclohepta[c]pyrazol-8(1H)-one (8). Yield 64%; mp: 247–248°C. IR (KBr, ν, cm^{-1}): 1635 (C=O), 1592 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 6.02 (s, 2H, OCH_2O), 6.89 (d, 1H, J = 8.2 Hz, 1,3-benzodioxol H-7′), 6.96 (d, 1H, J = 2.4 Hz, 1,3-benzodioxol H-4′), 7.31 (dd, 1H, J = 8.2, 2.4 Hz, 1,3-benzodioxol H-6′), 7.39–7.51 (m, 8H, benzene-H and tropone-H), 7.55 (d, 1H, J = 16.0 Hz, =CH), 7.77 (d, 1H, J = 16.4 Hz, =CH). ESI-HRMS calc. for $C_{23}H_{15}^{79}BrN_2NaO_3^+$, $[M+Na]^+$: 469.0159; found: 469.0164.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-5,7-dibromo-1-phenylcyclohepta[c]pyrazol-8(1H)-one (9). Yield: 42%; mp: 225–228°C. IR (KBr, ν, cm^{-1}): 1643 (C=O), 1595 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 6.05 (s, 2H, OCH_2O), 6.95 (d, 1H, J = 8.2 Hz, 1,3-benzodioxol H-7′), 7.12 (d, 1H, J = 2.0 Hz, 1,3-benzodioxol H-4′), 7.41–7.65 (m, 7H, benzene-H, =CH, and 1,3-benzodioxol H-6′), 7.83 (d, 1H, J = 16.0 Hz, =CH), 8.16 (d, 1H, J = 1.6 Hz, tropone H-6), 8.52 (d, 1H, J = 1.6 Hz, tropone H-4). ESI-HRMS calc. for $C_{23}H_{14}^{79}Br_2N_2NaO_3^+$, $[M+Na]^+$: 546.9264; found: 546.9273.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-5-bromo-1-phenylcyclohepta[c]pyrazol-8(1H)-one (10). Yield 51%; mp: 252–253°C. IR (KBr, ν, cm^{-1}): 1624 (C=O), 1587 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 5.99 (s, 2H, OCH_2O), 7.05 (d, 1H, J = 2.4 Hz, 1,3-benzodioxol H-4′), 7.13 (d, 1H, J = 11.0 Hz, tropone H-7), 7.26 (d, 1H, J = 8.2 Hz, 1,3-benzodioxol H-7′), 7.31–7.57 (m, 7H, benzene-H, tropone H-6, and 1,3-benzodioxol H-6′), 7.60 (d, 1H, J = 16.0 Hz, =CH), 7.81 (d, 1H, J = 16.0 Hz, =CH), 8.42 (d, 1H, J = 2.1 Hz, tropone H-4). ESI-HRMS calc. for $C_{23}H_{15}^{79}BrN_2NaO_3^+$ $[M+Na]^+$: 469.0159; found: 469.0152.

General procedure for the preparation of 3-[(E)-2-(1,3-benzodioxol-5-yl)vinyl]-8H-cyclohepta[d]isoxazol-8-one derivatives (11–13). A solution of compound **2**, **3**, or **4** (1 mmol) and hydroxylamine hydrochloride (2.0 mmols) in absolute ethanol (15 mL) was refluxed for 12 hours. After the reaction was over as monitored by TLC, the precipitate was collected and recrystallized from ethanol to give the products **11–13**.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-7-bromo-8H-cyclohepta[d]isoxazol-8-one (11). Yield 52%; mp: 275–276°C. IR (KBr, ν, cm^{-1}): 1640 (C=O), 1582 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 6.01 (s, 2H, OCH_2O), 6.98 (d, 1H, J = 2.1 Hz, 1,3-benzodioxol H-4′), 7.22 (d, 1H, J = 8.2 Hz, 1,3-benzodioxol H-7′), 7.33 (dd, 1H, J = 8.2, 2.1 Hz, 1,3-benzodioxol H-6′), 7.39 (d, 1H, J = 16.4 Hz, =CH), 7.57–7.64 (m, 3H, tropone H), 7.72 (d, 1H, J = 16.4 Hz, =CH). ESI-HRMS calc. for $C_{17}H_{10}^{79}BrNNaO_4^+$ $[M+Na]^+$: 393.9685; found: 393.9692.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-5,7-dibromo-8H-cyclohepta[d]isoxazol-8-one (12). Yield 49%; mp: 287–288°C. IR (KBr, ν, cm^{-1}): 1630 (C=O), 1575 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 5.98 (s, 2H, OCH2O), 6.81 (d, 1H, J = 8.0 Hz, 1,3-benzodioxol H-7′), 7.09 (d, 1H, J = 1.6 Hz, 1,3-benzodioxol H-4′), 7.31 (d, 1H, J = 16.0 Hz, =CH), 7.35 (dd, 1H, J = 8.0, 1.6 Hz, 1,3-benzodioxol H-6′), 7.77 (d, 1H, J = 16.0 Hz, =CH), 8.14 (d, 1H, J = 2.0 Hz, tropone H-6), 8.43 (d, 1H, J = 2.0 Hz, tropone H-4). ESI-HRMS calc. for $C_{17}H_9^{79}Br_2NNaO_4^+$ $[M+Na]^+$: 471.8789; found: 471.8783.

3-[(E)-2-(1,3-Benzodioxol-5-yl)vinyl]-5-bromo-8H-cyclohepta[d]isoxazol-8-one (13). Yield 48%; mp: 272–273°C. IR (KBr, ν, cm^{-1}): 1656 (C=O), 1590 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 6.10 (s, 2H, OCH_2O), 6.91 (d, 1H, J = 2.2 Hz, 1,3-benzodioxol H-4′), 6.97 (d, 1H, J = 8.1 Hz, 1,3-benzodioxol H-7′), 7.04 (d, 1H, J = 11.2 Hz, tropone H-7), 7.34 (d, 1H, J = 16.2 Hz, =CH), 7.43 (dd, 1H, J = 8.1, 2.2 Hz, 1,3-benzodioxol H-6′), 7.53 (dd, 1H, J = 11.2, 2.0 Hz, tropone H-6), 7.67 (d, 1H, J = 16.2 Hz, =CH), 8.40 (d, 1H, J = 2.1 Hz, tropone H-4). ESI-HRMS calc. for $C_{17}H_{10}^{79}BrNNaO_4^+$ $[M+Na]^+$: 393.9685; found: 393.9680.

Acknowledgments. The authors thank the Foundation of Liaoning Province Key Laboratory of Applied Chemistry (Grant No. 2008s001) for financial support.

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