ACS Combinatorial Science

RESEARCH ARTICLE

pubs.acs.org/acscombsci

Microwave-Assisted Solvent-Dependent Reaction: Chemoselective Synthesis of Quinoxalin-2(1*H*)-ones, Benzo[*d*]imidazoles and Dipeptides

Shu-Liang Wang,[†] Jie Ding,[†] Bo Jiang,[†] Yuan Gao,[*,‡] and Shu-Jiang Tu[*,†]

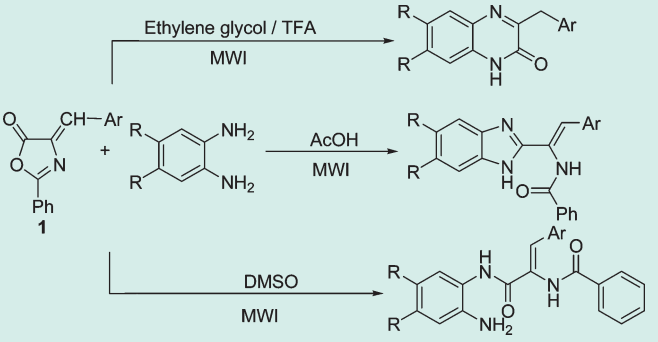
[†]School of Chemistry and Chemical Engineering, Key Laboratory of Green Synthetic Chemistry for Functional Materials, Xuzhou Normal University, Xuzhou, 221116, P. R. China

[‡]School of Chemistry and Chemical Engineering, Shenzhen University, P. R. China

Supporting Information

ABSTRACT: A microwave-assisted solvent-dependent chemoselective reaction dealing with 4-arylidene-2-phenyloxazol-5-ones and diverse ortho-diamines to achieve three types of molecular scaffolds, 3-benzylquinoxalin-2(1H)-ones, benzimidazole and β-amino dipeptides is reported. The procedures feature short reaction time, good to excellent yields, operational simplicity, as well as easily available starting materials. These compounds are of importance for organic chemistry and medicinal chemistry research.

KEYWORDS: solvent-dependent reaction, chemoselective synthesis, benzimidazole, 3-benzylquinoxalin-2(1*H*)-ones, β-amino dipeptides



INTRODUCTION

Chemoselective reactions are of obvious value as organic synthesis strives for ever-increasing levels of efficiency. In the past several years, many investigators have investigated the chemoselective control of reactions with metal catalysts,[1a−d] while relatively few papers describe solvent-dependent chemoselective reactions.[1e−g] However, since solvent plays an important role in all reactions, the development of solvent-dependent chemoselectivity is a worthy goal.

Quinoxaline is an important class of benzo-heterocyclic pyrazine compound and has been widely used as a key building block for pharmaceutical agents. Its derivatives are endowed with many pharmacological properties, such as hypoglycemic,[2] anti-inflammatory, antibacterial,[3] and anti-HIV[4] activity, as well as useful activities in conditions like depression and Parkinson's disease.[5] Quinoxalin-2(1*H*)-one as a class of important heterocyclic molecules in quinoxaline family has shown such biological activities as glutamate blocker,[6] treatment of sensorineural smell disorders,[7] DNA topoisomerase (Topo) II beta-inhibitor,[8] and antimycobacterial activity.[9] In addtion, benzimidazole derivatives also received much attention in clinical applications because of their diverse biological activity.[10] As a result, the synthesis of these molecules have attracted considerable attention.[11−13] Among them, the reaction of *o*-penylenediamine with 2-oxazoline-5-ones in BuOH led to the main quinoxalin-2(1*H*)-ones accompanied with butyl acrylate and benzimidazoles.[11] Subhashini et al. reported the synthesis of quinoxalin-2(1*H*)-ones accompanied with benzimidazoles in AcOH at room temperature using similar starting materials.[12] However, these reactions suffered from narrow scope of substrates and complex separation process as the different byproducts were generated. Moreover, the synthesis of benzimidazoles in AcOH employing similar reactants under heating conditions has also been described.[13] Thus these reactions described above could not be controlled to provide the quinoxalin-2(1*H*)-ones and benzimidazoles, respectively. Therefore, our concern was whether the generation of quinoxalin-2(1*H*)-ones or benzimidazoles can be controlled using the same starting materials by varying the reaction conditions. Delightedly, we found chemoselectivity of the reaction could be realized by changing acidity of reaction media, and three different types of products with good to excellent yields were generated, respectively. We therefore describe here novel solvent-controlled reactions for the chemoselective synthesis of quinoxalin-2(1*H*)-ones **3**, benzo[*d*]imidazoles **4**, and dipeptides **5** from 4-arylidene-2-phenyloxazol-5-ones **1** (Figure 1) and diverse ortho-diamines **2** (Figure 2) (Scheme 1).

RESULT AND DISCUSSION

Choosing an appropriate reaction medium is of crucial importance not only for successful microwave-promoted (MW) synthesis, but also for the effective control of chemoselective reactions. To choose the optimum solvent, the microwave-assisted reaction of oxazol-5(4*H*)-one **1**{*8*} with benzene-1,2-diamine **2**{*1*} was

Received: August 1, 2011
Published: August 04, 2011

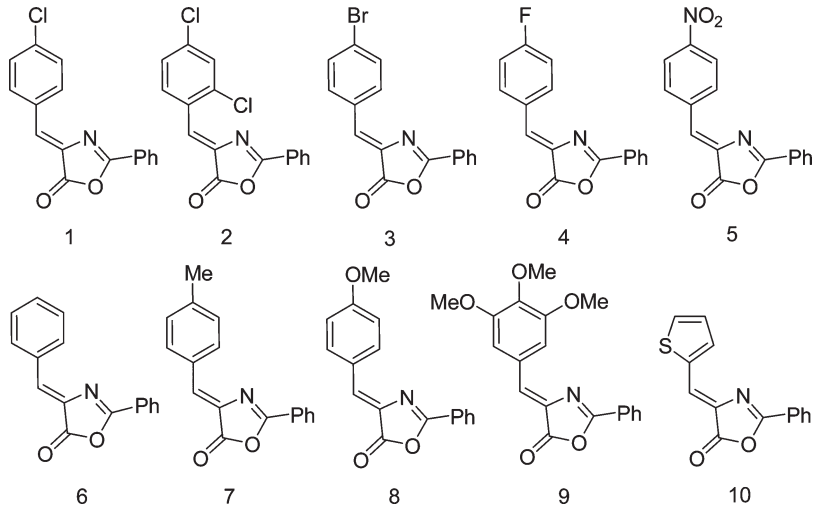


Figure 1. Diversity of 4-arylidene-2-phenyloxazol-5(4*H*)-ones **1**{*1*−*10*}.

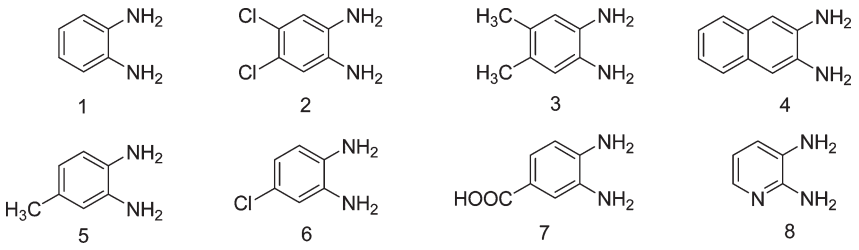
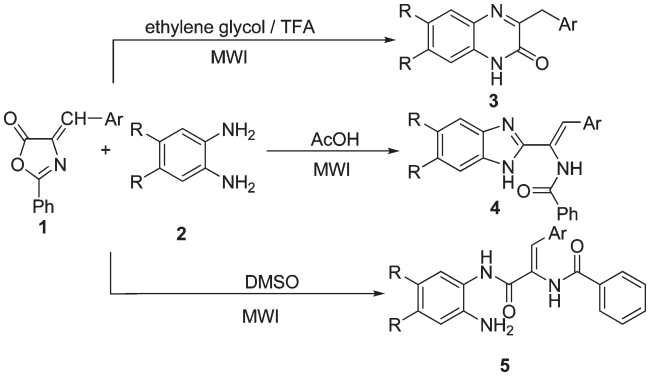


Figure 2. Diversity of aromatic diamines **2**{*1*−*8*}.

Scheme 1. Solvent-Dependent Chemoselective Synthesis of Compound 3, 4, and 5



examined at 120 °C in different solvents, such as ethanol, ethylene glycol, H_2O, *N*,*N*-dimethylformamide (DMF), AcOH, dimethyl sulfoxide (DMSO), and a mixture of trifluoroacetic acid (TFA) and ethylene glycol. All the reactions were carried out under microwave irradiation. The results of the screening of solvents are presented in Table 1 (entries 1−7). As shown in Table 1, when ethanol, glycol, H_2O, and DMF were selected as the solvent, the compound **4**{*8*,*1*} was obtained accompanied with a small quantity of **5**{*8*,*1*}. While acetic acid was used as the solvent, only benzimidazole **4**{*8*,*1*} was obtained with 85% yield

Table 1. Reaction of 1{*8*} with 2{*1*} in Different Solvents (Reaction Time = 15 min)

		yield[b] (%)		
entry	solvent[a]	**3**{*8*,*1*}	**4**{*8*,*1*}	**5**{*8*,*1*}
1	EtOH	16	30	0
2	glycol	24	41	0
3	H_2O	0	30	0
4	DMF	19	53	0
5	AcOH	0	85	0
6	DMSO	0	0	81
7	glycol + TFA[c]	88	0	0

[a] 2.0 mL reaction volume. [b] Isolated yields. [c] Mixture of trifluoroacetic acid (TFA, 2 equiv. relative to reagents) in ethylene glycol.

(Table 1, entry 5), whereas the reaction in cosolvent of ethylene glycol and TFA gave quinoxalin-2(1*H*)-one **3**{*8*,*1*} in 88% yield (Table 1, entry 7). Under aprotic conditions (DMSO solvent), only the dipeptide **5**{*8*,*1*} was observed (Table 1, entry 6). Thus, the reaction could be directed cleanly to three different products, quinoxalin-2(1*H*)-ones **3**, benzimidazole **4** or dipeptides **5**, by changing the reaction medium (Scheme 2).

Scheme 2 shows a proposed reaction pathway. The dipeptides **5** are obtained from the expected initial condensation reaction of diamines with 4-arylidene-2-phenyloxazol-5(4*H*)-ones, and do not undergo cyclization in the absence of acid. The ability of acetic and trifluoroacetic acids to direct the subsequent processes

dx.doi.org/10.1021/co2001247 |*ACS Comb. Sci.* 2011, 13, 572–577

Scheme 2. Reasonable Mechanism for the Production of 3, 4, and 5

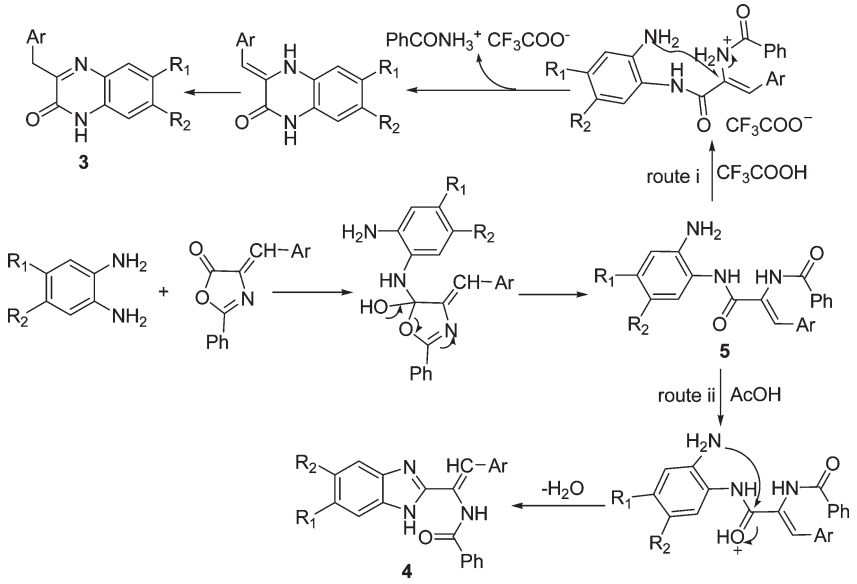


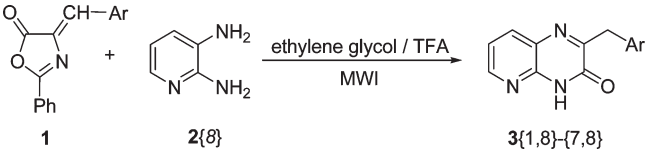
Table 2. Syntheses of Quinoxalin-2(1*H*)-ones 3

entry	product	time/min	yield/%
1	3{*1,1*}	14	83
2	3{*2,1*}	15	85
3	3{*5,1*}	15	88
4	3{*6,1*}	14	86
5	3{*7,1*}	16	82
6	3{*8,1*}	16	88
7	3{*10,1*}	13	80
8	3{*1,2*}	14	84
9	3{*2,2*}	13	85
10	3{*7,2*}	15	83
11	3{*8,2*}	16	86
12	3{*9,2*}	18	79
13	3{*2,3*}	15	82
14	3{*3,3*}	15	83
15	3{*7,3*}	15	84
16	3{*8,3*}	15	89
17	3{*10,3*}	14	80
18	3{*3,4*}	15	90
19	3{*1,8*}	14	81
20	3{*2,8*}	14	80
21	3{*3,8*}	16	83
22	3{*6,8*}	15	82
23	3{*7,8*}	16	84

to benzimidazole and quinoxalinone systems, respectively, is not yet understood. The different acids apparently provide different degrees of protonation of the competing amide groups, leading to 5- or 6-membered ring closure as shown.

Under these optimized chemoselective conditions, a series of 3-benzylquinoxalin-2(1*H*)-ones, poly substituted benzo[*d*]imidazoles and *β*-amino dipeptides were selectively synthesized with the reaction of 4-arylideneoxazol-5-ones **1** and diamines **2** in

Scheme 3. Reaction between 4-Arylideneoxazol-5-ones and Pyridyldiamine



the appropriate solvent under microwave irradiation. Table 2 (entries 1−7) shows an exploration of the 4-arylidene-2-phenyloxazol-5-one substrate scope in a reaction with 1,2-phenylenediamine in the presence of TFA. The results indicated that both electron-withdrawing and electron-donating functional groups on the 4-arylidene aromatic ring were well tolerated in the production of compounds **3**. Moreover, the 2-thienyl substituted 2-phenyloxazol-5-one (Table 2, entry 7) also displayed high reactivity under this standard condition. Table 2 (entries 8−18) also shows excellent results with a set of 4-arylidene-2-phenyloxazol-5-ones and the additional ortho-diamines **2**{*2*}, **2**{*3*}, and **2**{*4*}. In all these cases, the reactions proceeded steadily to produce the functionalized 3-benzylquinoxalin-2(1*H*)-ones in good yields of 79−90%. All new compounds were characterized by IR, ^{1}H NMR, and HRMS (ESI) spectroscopy, and the structure of **3**{*8,1*} was confirmed by single-crystal X-ray diffraction analysis (Supporting Information).

The reaction of the unsymmetrical pyridyldiamine **2**{*8*} with **1**{*1,2,3,6,7*} gave a single regioisomer of quinoxalinone **3**-{*1,8*}−**3**{*7,8*} (Table 2, entries 19−23) (Scheme 3), and the structure of **3**{*1,8*} was confirmed by single-crystal X-ray diffraction analysis. Because of its electronegativity, the pyridyl nitrogen atom should deactivate the nucleophilicity of the o-amino group to a greater extent than the *m*-amino group. However, the strong acid used in these reactions should protonate the pyridyl nitrogen, leading to greater deactivation of the *m*-amino group.[14] So, in the present of TFA, the *o*-amino group preferentially attacks

dx.doi.org/10.1021/co2001247 |*ACS Comb. Sci.* 2011, 13, 572–577

Table 3. Syntheses of Benzimidazoles 4

entry	product	time/min	yield/%
1	4{*1,1*}	15	92
2	4{*2,1*}	14	87
3	4{*5,1*}	14	89
4	4{*6,1*}	14	76
5	4{*7,1*}	15	82
6	4{*8,1*}	15	85
7	4{*2,2*}	13	86
8	4{*9,2*}	15	82
9	4{*1,5*}	15	85
10	4{*5,5*}	15	82
11	4{*2,6*}	16	83
12	4{*3,6*}	16	81
13	4{*5,6*}	15	86
14	4{*9,6*}	16	78

the 4-arylidene-5-one **1** to afford the ring opened compound **5**, which is subsequently converted to the quinoxalinones **3**.

The ability of acetic acid to change the pathway of the reaction to give benzimidazoles **4** was validated with a series of components as shown in Table 3. As before, both electron-withdrawing and -donating groups were tolerated on the 4-arylidene-2-phenyloxazol-5-one substrate. Moreover, monosubstituted ortho-diamines **2**{*5* or *6*} also resulted in desired products **4** in good yields. The structural elucidation and the attribution of relative stereochemistry were unequivocally determined by NMR analysis and X-ray diffraction of single crystal that was obtained by slow evaporation of the solvent, as in the case of benzimidazoles **4**{*1,1*}.

Similarly, intermediates **5** could be accessed in high yields in DMSO solvent without the addition of acid, with the same range of substrate tolerance as observed in the preparations of **3** and **4** (Table 4). The use of 3,4-diaminobenzoic acid **2**{*7*} gave only one of the two possible isomers in **5**{*7,7*} and **5**{*8,7*} with high regioselectivity (Table 4, entries 11−12). This is attributed to the greater nucleophilicity of the amino group in the meta position relative to the carboxyl group, resulting in initial attack by that amine center.[14] It is worthy noted that the dipeptides with wide spectrum of important bioactivities were synthesized by screening the reaction solvents, which were significant intermediates for pharmaceutical design and research.[15]

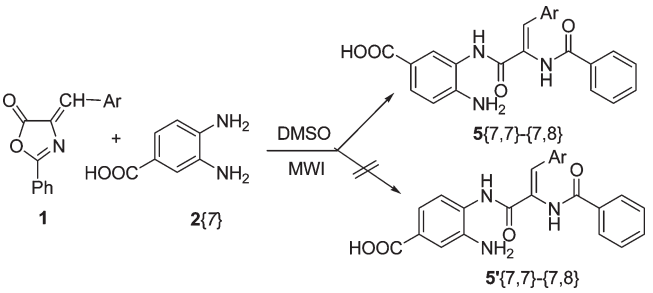
To substantiate the intermediacy of **5** in the production of **3** and **4** (Scheme 2), isolated **5**{*6,1*} was subjected to the two acidic conditions (TFA in ethylene glycol and AcOH). The expected products, **3**{*6,1*} and **4**{*6,1*}, respectively, were isolated cleanly. Furthermore, the addition of TFA to AcOH redirected the reaction to **3**{*6,1*}, favoring six-membered cyclization in the presence of the stronger acid.

In conclusion, poly substituted 3-benzylquinoxalin-2(1*H*)-ones, benzo[*d*]imidazoles, and β-amino dipeptides were prepared from the same substrates in convenient and highly selective fashion when different solvents were used, varying the strength of the acidic reaction environment. The reactions are fast and can be finished within 13−16 min with good to excellent chemical yields and chemo- and regioselectivity that avoided tedious workup and purification steps. Furthermore, the series of compounds produced are of general interest for their chemical properties and potential physiological activity, studies which are in progress in our laboratory.

Table 4. Syntheses of Dipeptides 5

entry	product	time/min	yield/%
1	5{*5,1*}	15	81
2	5{*6,1*}	14	82
3	5{*8,1*}	15	84
4	5{*10,1*}	15	72
5	5{*1,2*}	16	82
6	5{*2,2*}	15	83
7	5{*3,2*}	14	80
8	5{*5,2*}	15	76
9	5{*7,2*}	15	73
10	5{*10,2*}	13	70
11	5{*7,7*}	15	79
12	5{*8,7*}	15	82

Scheme 4. Reaction between 4-Arylideneoxazol-5-ones and 3,4-Diaminobenzoic Acid



EXPERIMENTAL PROCEDURES

Microwave irradiation was carried out with microwave oven Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in parts per million relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Typical Procedure for the Preparation of 3-(4-Methoxybenzyl)quinoxalin-2(1*H*)-one 3{*8,1*}. In a 10-mL Emrys reaction vial, 4-(4-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (0.28 g, 1 mmol), benzene-1,2-diamine (0.11 g, 1 mmol), TFA (0.23 g, 2 mmol), and ethylene glycol (1.5 mL) were mixed and then capped. (The automatic mode stirring helped the mixing and uniform heating of the reactants.) The mixture was heated for 16 min at 120 °C under microwave irradiation. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was poured into water and neutralized with 10% NaOH, and then collected by Büchner filtration, subsequently washed with two different solvents of ethanol and ethylether in sequence to give the pure yellow solid (0.23 g, yield 88%). mp: 188−189 °C.

^1H NMR (400 MHz, DMSO) (δ, ppm): 12.38 (s, 1H, NH), 7.72 (d, J = 8.0 Hz, 1H, ArH), 7.50−7.46 (m, 1H, ArH),

dx.doi.org/10.1021/co2001247 |*ACS Comb. Sci.* 2011, 13, 572–577

7.28−7.23 (m, 4H, ArH), 6.85 (d, J = 8.8 Hz, 2H, ArH), 4.05 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3).

IR (KBr): 3154, 3009, 2957, 2835, 2783, 2064, 1907, 1661, 1556, 1506, 1431, 1245, 1173, 1036, 905, 820, 751 cm^{-1}.

HRMS (ESI): m/z $[M + H]^+$ $C_{16}H_{15}N_2O_2$ 289.0953; found 289.0949.

(*Z*)-*N*-(1-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(4-methoxyphenyl)-vinyl)benzamide 4{*8,1*}. In a 10-mL Emrys reaction vial, 4-(4-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (0.28 g, 1 mmol), benzene-1,2-diamine (0.11 g, 1 mmol) and AcOH (2.0 mL) were mixed and then capped (The automatic mode stirring helped the mixing and uniform heating of the reactants). The mixture was heated for 15 min at 120 °C under microwave irradiation. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was mixed into water then collected by Büchner filtration and subsequently washed with two different solvents of ethanol and ethylether in sequence to give the pure yellow solid (0.32 g, yield 85%). mp: 258−260 °C

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.45 (s, 1H, NH), 10.19 (s, 1H, NH), 8.11 (d, J = 7.2 Hz, 2H, ArH), 7.66−7.62 (m, 2H, ArH), 7.57 (t, J = 7.2 Hz, 3H, ArH), 7.52 (d, J = 6.0 Hz, 1H, ArH), 7.17−7.15 (m, 2H, ArH), 6.95 (d, J = 8.8 Hz, 2H, ArH),3.75 (s, 3H, OCH_3).

IR (KBr): 3221, 3060, 2934, 2836, 2768, 2638, 1647, 1604, 1509, 1481, 1421, 1302, 1255, 1177, 1116, 1030, 984, 909, 825, 744, 707 cm^{-1}.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_2$ 370.-1556; found 370.1553.

(*Z*)-*N*-(3-(2-Aminophenylamino)-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)benzamide 5{*8,1*}. In a 10-mL Emrys reaction vial, 4-(4-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (0.28 g, 1 mmol), benzene-1,2-diamine (0.11 g, 1 mmol), and DMSO (2.0 mL) were mixed and then capped. The mixture was heated for 15 min at 110 °C under microwave irradiation. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was added into water then collected by Büchner filtration and subsequently washed with two different solvents of ethanol and ethylether in sequence to give the pure yellow solid (0.31 g, yield 81%). mp: 197−198 °C

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 10.13 (s, 1H, NH), 9.44 (s, 1H, NH), 8.06 (d, J = 7.6 Hz, 2H, ArH), 7.62−7.60 (m, 3H, ArH), 7.53 (t, J = 7.2 Hz, 2H, ArH), 7.22 (s, 1H, ArH), 7.03 (d, J = 7.6 Hz, 1H, ArH), 6.95 (d, J = 8.4 Hz, 1H, ArH), 6.71 (d, J = 8.0 Hz, 1H, ArH), 6.55 (t, J = 7.6 Hz, 1H, CH), 4.93 (s, 2H, NH_2), 3.76 (s, 3H, OCH_3).

IR (KBr): 3354, 3252, 3034, 2960, 2837, 1641, 1603, 1512, 1482, 1304, 1254, 1179, 1030, 923, 831, 750 cm^{-1}.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{21}N_3O_3$ 388.1661; found 388.1653.

Examination of Reaction Mechanism. In a 10-mL Emrys reaction vial, (*Z*)-*N*-(3-(2-aminophenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide 5{*6,1*} (1.0 mmol), TFA (0.23 g, 2 mmol) and ethylene glycol (1.5 mL) were mixed and then capped. (The automatic mode stirring helped the mixing and uniform heating of the reactants.) The mixture was heated for 14 min at 120 °C under microwave irradiation. The subsequent operating procedure was same as described above to give corresponding 3{*6,1*}.

In a 10-mL Emrys reaction vial, (*Z*)-*N*-(3-(2-aminophenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide 5{*6,1*}-(1.0 mmol) and AcOH (2.0 mL) were mixed and then capped. The mixture was heated for 14 min at 120 °C under microwave irradiation. The subsequent operating procedure was same as described above to give corresponding 4{*6,1*}.

In a 10-mL Emrys reaction vial, (*Z*)-*N*-(3-(2-aminophenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide 5{*6,1*}(1.0 mmol), TFA (0.23 g, 2 mmol), and AcOH (2.0 mL) were mixed and then capped. (The automatic mode stirring helped the mixing and uniform heating of the reactants.) The mixture was heated for 14 min at 120 °C under microwave irradiation. The subsequent operating procedure was same as described above to also give corresponding 3{*6,1*}.

■ ASSOCIATED CONTENT

Supporting Information. Additional experimental details and crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: 0086-516-83500065. Fax: 0086-516-83500065. E-mail: laotu@xznu.edu.cn.

■ ACKNOWLEDGMENT

We are grateful to financial support from the National Science Foundation of China (No. 21072163 and 21002083), Sci. Foundation in Interdisciplinary Major Res. Project of XZNU (No. 09XKXK01), and PAPD of Jiangsu Higher Education Institutions.

■ REFERENCES

(1) (a) Padwa, A.; Austin, D. J. Transition-metal-catalyzed reactions of α-diazo carbonyl compounds: Effect of ligands on chemoselectivity. *Angew. Chem.* **1994**, *106*, 1881–1899. (b) Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. Novel chemoselectivity and stereochemical aspects of nickel-catalyzed [2 + 2+2] cycloadditions. *J. Am. Chem. Soc.* **1999**, *121*, 476–477. (c) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. Controlling chemoselectivity in vinyl and allylic C−X bond activation with palladium catalysis: A pK_a-based electronic switch. *J. Am. Chem. Soc.* **2002**, *124*, 1288–1294. (d) Lebel, H.; Paquet, V. Highly chemoselective rhodium-catalyzed methylenation of fluorine-containing ketones. *Org. Lett.* **2002**, *4*, 1671–1674. (e) Tu, S. J.; Jiang, B.; Jia, R. H.; Zhang, J. Y.; Yao, C. S.; Shi, F. An efficient and chemoselective synthesis of N-substituted 2-aminopyridines via a microwave-assisted multicomponent reaction. *Org. Biomol. Chem.* **2007**, *5*, 355–359. (f) Wang, J.; Mason, R.; Derveer, D. V.; Feng, K.; Bu, X. R. Convenient preparation of a novel class of imidazo[1,5-*a*]pyridines: Decisive role by ammonium acetate in chemoselectivity. *J. Org. Chem.* **2003**, *68*, 5415–5418. (g) Lin, M. L.; Maddirala, S. J.; Liu, R. S. Solvent-dependent chemoselectivity in ruthenium-catalyzed cyclization of iodoalkyne-epoxide functionalities. *Org. Lett.* **2005**, *7*, 1745–1748.

(2) (a) Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Dunning, B. E.; Mangold, B. L.; Mone, M. D.; Russell, M. E.; Weldon, S. C.; Hughes, T. E. 1-[2-[(5-Cyanopyridin-2-yl)amino]ethylamino]acetyl-2-(*S*)-pyrrolidinecarbonitrile: A potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J. Med. Chem.* **2002**, *45*, 2362–2365. (b) Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Burkey, B. F.; Dunning, B. E.; Prasad, K.; Mangold, B. L.; Russell, M. E.; Hughes, T. E. 1-[[(3-Hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(*S*)-pyrrolidine: A potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J. Med. Chem.* **2003**, *46*, 2774–2789.

(3) (a) O'Brien, T.; Fahr, B. T.; Sopko, M. M.; Lam, J. W.; Waal, N. D.; Raimundo, B. C.; Purkey, H. E.; Pham, P.; Romanowski, M. J. Structural analysis of caspase-1 inhibitors derived from tethering. *Acta Crystallogr. F* **2005**, *61*, 451–458. (b) Allen, D. A.; Pham, P.; Choong, I. C.; Fahr, B.; Burdett, M. T.; Lew, W.; DeLano, W. L.; Gordon, E. M.; Lam, J. W.; O'Brien, T.; Lee, D. Identification of potent and novel small-molecule inhibitors of caspase-3. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3651–3655.

(4) (a) Kleim, J. P.; Bender, R.; Kirsch, R.; Meichsner, C.; Paessens, A.; Rosner, M.; Rubsamen Waigmann, H.; Kaiser, R.; Wichers, M.; Schneweis, K. E.; Winkler, I.; Riess, G. Preclinical evaluation of HBY 097, a new nonnucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 replication. *Antimicrob. Agents Chemother.* **1995**, *39*, 2253–2257. (b) Gris, J.; Glisoni, R.; Fabian, L.; Fernandez, B.; Moglioni, A. G. Synthesis of potential chemotherapeutic quinoxalinone derivatives by biocatalysis or microwave-assisted Hinsberg reaction. *Tetrahedron Lett.* **2008**, *49*, 1053–1056.

(5) Cesura, A. M.; Pletscher, A. The new generation of monoamine oxidase inhibitors. *Prog. Drug Res.* **1992**, *38*, 171–297.

(6) Perez, C.; Lopez, de C. A.; Bello, J. Induction of micronuclei in V-79 cells after combined treatments with heterocyclic aromatic amines. *Food Chem. Toxicol.* **2002**, *40*, 1463–1467.

(7) Quint, C.; Temmel, A. F.; Hummel, T.; Ehrenberger, K. The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Oto-laryngol.* **2002**, *122*, 877–881.

(8) Mensah-Osman, E. J.; AL-Katib, A. M.; Dandashi, M. H.; Mohammad, R. M. 2-[4-(7-Chloro-2-quinoxalinyloxy)phenoxy]-propionic acid (XK469) inhibition of topoisomerase IIβ is not sufficient for therapeutic response in human Waldenstrom's macroglobulinemia xenograft model. *Mol. Cancer Ther.* **2002**, *1*, 1315–1320.

(9) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. Synthesis and antimycobacterial activity of pyrazine and quinoxaline derivatives. *J. Med. Chem.* **2002**, *45*, 5604–5606.

(10) (a) Jordan, A. D.; Vaidya, A. H.; Rosenthal, D. I.; Dubinsky, B.; Kordik, C. P.; Sanfilippo, P. J.; Wu, W. N.; Reitz, A. B. Potential anxiolytic agents. Part 4: Novel orally-active N5-substituted pyrido-[1,2-*a*]benzimidazoles with high GABA-A receptor affinity. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2381–2386. (b) Orjales, A.; Mosquera, R.; Labeaga, L.; Rodes, R. New 2-piperazinylbenzimidazole derivatives as 5-HT3 antagonists. Synthesis and pharmacological evaluation. *J. Med. Chem.* **1997**, *40*, 586–593. (c) Evers, D. L.; Komazin, G.; Shin, D.; Hwang, D. D.; Townsend, L. B.; Drach, J. C. Interactions among antiviral drugs acting late in the replication cycle of human cytomegalovirus. *Antiviral Res.* **2002**, *56*, 61–72.

(11) Jellal, M.; Ramli, Y.; Moussaif, A.; Rodi, Y. K.; Fifani, J.; Essassi, E. M.; Pierrot, M. Study of the condensation of *o*-phenylenediamine with 4-arylideneoxazolin-5-ones in *n*-butanol. *J. Soc. Chim. Tunis.* **2005**, *7*, 19–26.

(12) Subhashini, N. J. P.; Hanumanthu, P. Condensation of *o*-phenylenediamines with azlactones. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26B*, 32–35.

(13) (a) Tikdari, A. M.; Mukerjee, A. K. Aminolysis of unsaturated azlactones with *o*-phenylenediamine/*o*-aminophenol and cyclization of the resultant anilides. *J. Prakt. Chem.* **1988**, *330*, 647–649. (b) Tikdari, A. M.; Mukerjee, A. K. Reaction of *o*-phenylenediamine with 2-oxazolin-5-ones. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26B*, 73–74. (c) Habib, O. M. O.; Hassan, H. M.; Moawad, E. B. Synthesis and reactions of some new 2-[4′-(3″,4″-xylenesulfonamido) phenyl]-4-arylmethyleneoxazolin-5-ones. *J. Prakt. Chem.* **1986**, *328*, 295–300. (d) Harb, A. F. A.; Zayed, S. E.; El-Maghraby, A. M.; Metwally, S. A. Behavior of *o*-phenylenediamine and *o*-aminothiophenol with azlactones. A new synthesis of some benzimidazole and benzothiazole derivatives. *Heterocycles* **1986**, *24*, 1873–1881. (e) Kidwai, M.; Saxena, S.; Mohan, R. A new method for the synthesis of heterocycles from *o*-phenylenediamine. *J. Korean Chem. Soc.* **2005**, *49*, 288–291. (f) Ferro, S.; Rao, A.; Zappala, M.; Chimirri, A.; Barreca, M. L.; Witvrouw, M.; Debyser, Z.; Monforte, P. Synthesis of new potential HIV-1 integrase inhibitors. *Heterocycles* **2004**, *63*, 2727–2734.

(14) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey 2007; pp 356−394.

(15) (a) Strom, K.; Sjogren, J.; Broberg, A.; Schnurer, J. Lactobacillus plantarum MiLAB 393 produces the antifungal cyclic dipeptides cyclo(L-Phe-L-Pro) and cyclo(L-Phe-*trans*-4-OH-L-Pro) and 3-phenyllactic acid. *Appl. Environ. Microbiol.* **2002**, *68*, 4322–4327. (b) Faden, A. I.; Movsesyan, V. A.; Knoblach, S. M.; Ahmed, F.; Cernak, I. Neuroprotective effects of novel small peptides in vitro and after brain injury. *Neuropharmacol.* **2005**, *49*, 410–424. (c) Tang, X.; Fan, L.; Yu, H.; Liao, Y.; Yang, D. Chin. The synthesis and structure of 1-[3-{(2-hydroxybenzylidene)amino}phenyl]ethanone. *J. Org. Chem.* **2009**, *29*, 595–600. (d) Lucietto, F. R.; Milne, P. J.; Kilian, G.; Frost, C. L.; Van De Venter, M. The biological activity of the histidine-containing diketopiperazines cyclo(His-Ala) and cyclo(His-Gly). *Peptides* **2006**, *27*, 2706–2714.