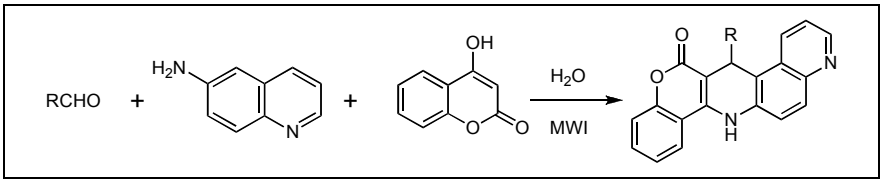
A Highly Efficient Microwave-assisted Synthesis of Chromeno-[3,4-*b*][4,7]phenanthroline Derivatives Through Multicomponent Reactions in Water

Qiya Zhuang, Dianxiang Zhou, Shujiang Tu,* Chunmei Li, Longji Cao, Qingqing Shao

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu, 221116, P. R. China

Received October 22, 2007



A short and simple synthesis of chromeno[3,4-*b*][4,7]phenanthroline derivatives was accomplished by three-component reactions involving an aromatic aldehyde, 6-aminoquinoline and 4-hydroxycoumarin in water, under microwave irradiation without use of any catalyst. This protocol has the advantages of short reaction time, high yields, low cost and being environmental-friendly as well as easy operation.

J. Heterocyclic Chem., **45**, 831 (2008).

INTRODUCTION

Multicomponent reactions, in which multiple reactions are combined into one synthetic operation, have been extensively used in synthetic chemistry for the formation of carbon-carbon and carbon-heteroatom bonds [1]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings both of solvents and of reagents. The use of water as a solvent has many advantages in organic synthesis, both from economical and from environmental points of view [2]. Water has therefore become an attractive medium for many organic reactions, not only as the need for drying reactants, expensive catalysts, and solvents can be circumvented, but also for its unique reactivity and selectivity [3,4]. Many important types of heterocyclic compounds, such as triazines [5], acridines [6], quinolines [7], pyridines [8], indoles [9], pyrazines [10], furans [11], and pyrimidines [12], have been synthesized in aqueous medium. The synthesis of new and important types of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.

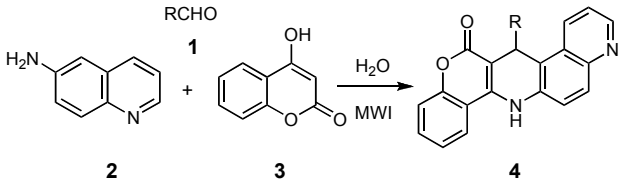
Chromenes and their derivatives are important compounds, which are found to possess antiestrogenic activity and are devoid of any agonistic activity [13], and are evaluated for potassium channel opening and hypotensive activities [14], vasodilator and antihypertensive activities [15], β-adrenolytic activity [16], antimicrobial activity [17], and biological activity of high-affinity retinoic acid receptor antagonist [18].

Compounds of 4,7-phenanthroline series possess high and versatile biological activity, such as antiallergic and antitumor activities [19]. And they are also used as inhibitors of the enzymes [20] and fungicides [21]. Hence, the preparation of this heterocyclic unit has gained much attention.

Chromenes [22] and 4,7-phenanthroline [23] derivatives have been reported widely in the literature. For example, Martinez [24] and co-works have reported the reaction of aldehydes, β-naphthylamine and 4-hydroxycoumarin in ethanol. Their protocol have inevitable drawbacks such as: (i) narrow application scope of substrates, (ii) using organic solvent and low yields, (iii) long reaction time and two-step reaction. Therefore, it is urgent to develop a more efficient and greener protocol to prepare similar skeleton compounds.

Herein, we describe a simple multicomponent reaction involving an aldehyde **1**, 6-aminoquinoline **2**, and 4-hydroxycoumarin **3** in water under microwave irradiation (MWI) without use of any catalyst to synthesize the chromeno[3,4-*b*][4,7]phenanthroline derivatives **4** (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for a successful organic synthesis. To search for the optimal solvent, the microwave-assisted reaction

between 4-chlorobenzaldehyde (**1b**, 1.0 mmol), 6-aminoquinoline (**2**, 1.0 mmol) and 4-hydroxycoumarin (**3**, 1.0 mmol) was examined in ethylene glycol, glacial acetic acid, ethanol, *N*,*N*-dimethylformamide and water as solvents (2.0 mL) at 100 °C, respectively. All the reactions were carried out at the maximum power of 250 W and the results are summarized in Table 1.

As can be seen in Table 1, the reactions with ethylene glycol or water as the solvent gave higher yields and required shorter reaction times than those with AcOH, DMF or EtOH (Table1, entries 1–5). Water was thus chosen as the solvent for all further microwave-assisted reactions, as it is environmentally friendly and allows toxic organic reagents to be avoided.

To further optimize the reaction temperature, the same three reagents were allowed to react in water at temperatures ranging from 110 to 150 °C, with an increment of 10 °C each time. The results are shown in Table 1. The yield of product **4b** was increased and the reaction time was shortened as the temperature was increased from 110 °C to 140 °C (Table 1, entries 6-9). However, further increase of the temperature to 140-150 °C failed to improve the yield of product **4b** (Table 1, entry 10). Therefore, 140 °C was chosen as the reaction temperature for all further microwave-assisted reactions.

Table 1

Optimization of reaction conditions of compound **4b**.

Entry	Solvent	T / °C	Time / min	Yield / %
1	Glycol	100	9	85
2	AcOH	100	10	80
3	EtOH	100	12	75
4	DMF	100	11	81
5	water	100	9	84
6	water	110	8	86
7	water	120	7	89
8	water	130	7	91
9	water	140	6	93
10	water	150	6	92

The maximum power of microwave irradiation was optimized by carrying out the same reaction for the synthesis of **4b** at powers of 100, 150, 200, 250 and 300 W respectively, using water as solvent at 140 °C. When the power was at 100–200 W, the times taken for the temperature to reach 140 °C were too long. Microwave irradiation at 250 W gave the highest yield and the maximum temperature reached during the reaction was 141 °C. Therefore, a microwave power of 250 W was chosen as the optimal power.

Under these optimized reaction conditions [water, 140 °C, 250 W (Maximum power)] a series of chromeno[3,4-*b*][4,7]phenanthroline derivatives **4** were synthesized. The results are summarized in Table 2. As shown in Table 2, this methodology can be applied not only to aromatic aldehydes either with electron-donating groups (such as alkoxyl groups) or with electron-withdrawing groups (such as nitro or halide groups), but also to heterocyclic aldehyde, such as thiophene-2-carbaldehyde (Table 2, entry 13), with excellent yields under same conditions, so we conclude that the electronic nature of the substituents has no significant effect on this reaction.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of chromeno[3,4-*b*][4,7]phenanthroline derivatives **4** could be explained by the possible mechanism presented in Scheme 2.

All the products in this study were characterized by mp and by IR and ^{1}H NMR spectroscopy, as well as by elemental analyses.

In summary, we have developed a simple three-component reaction involving an aldehyde, 6-aminoquinoline, and 4-hydroxycoumarin for the synthesis of chromeno[3,4-*b*][4,7]phenanthroline derivatives in high-temperature water under microwave irradiation condition. This green procedure offers several advantages including operational simplicity, clean reactions, increased safety for small-scale high-speed synthesis, and minimal environmental impact that makes it a useful and attractive process for the synthesis of these compounds. The new series of chromeno[3,4-*b*][4,7]phenanthroline derivatives may provide new classes of biologically active compounds for biomedical screening. This work is currently in progress and the results will be reported in due course.

EXPERIMENTAL

Microwave irradiation was carried out with an Emrys™ Creator microwave oven from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken with a FT-IR-Tensor 27 spectrometer in KBr pellets and are reported in cm^{-1}. ^{1}H NMR spectra were measured with a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Elemental analysis was determined with a Perkin-Elmer 240c elemental analysis instrument.

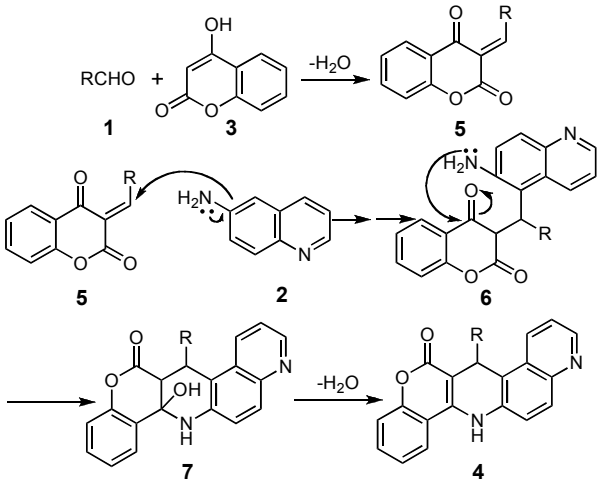
General procedure for the one-pot synthesis of chromeno-[3,4-*b*][4,7]phenanthroline derivatives 4 in water under microwave irradiation condition. Typically, in a 10-mL Emrys™ reaction vial, aldehydes **1** (1 mmol), 6-aminoquinoline **2** (1 mmol), 4-hydroxycoumarin **3** (1 mmol) and water (2 mL) were mixed and then capped. The mixture was irradiated for a given time at 140 °C under microwave irradiation (initial power 200 W and maximum power 250W). Upon completion, monitored by TLC, the reaction mixture was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure chromeno[3,4-*b*][4,7]-phenanthroline derivatives **4**.

Table 2

Synthesis of **4** in water under microwave irradiation at 140 °C

Entry	Product	R	Time/min	Yield/ %	Mp / ° C
1	**4a**	4-FC_6H_4	6	93	>300
2	**4b**	4-ClC_6H_4	6	93	>300
3	**4c**	4-BrC_6H_4	5	94	>300
4	**4d**	4-$CH_3OC_6H_4$	5	95	>300
5	**4e**	4-$NO_2C_6H_4$	6	94	>300
6	**4f**	3-$NO_2C_6H_4$	5	95	>300
7	**4g**	4-$CH_3C_6H_4$	5	95	>300
8	**4h**	C_6H_5	5	94	>300
9	**4i**	3,4-$(CH_3O)_2C_6H_3$	5	94	>300
10	**4j**	2,4-$Cl_2C_6H_3$	6	93	>300
11	**4k**	3,4-$OCH_2OC_6H_3$	6	94	>300
12	**4l**	4-OH-3-$NO_2C_6H_3$	5	95	>300
13	**4m**	thien-2-yl	5	95	>300

Scheme 2



14-(4-Fluorophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4a). This compound was obtained according to the above general procedure; ir (potassium bromide): 3232, 3184, 3065, 1655, 1635, 1604, 1570, 1450, 1398, 1246, 1098, 781, 616 cm^{-1}; ^{1}Hnmr: δ 10.24 (s, 1H, NH), 8.73-8.74 (m, 1H, ArH), 8.39-8.44 (m, 2H, ArH), 7.95-8.02 (m, 2H, ArH), 7.66 (t, 1H, ArH, J = 7.6 Hz), 7.43-7.50 (m, 2H, ArH), 7.39-7.40 (m, 3H, ArH), 7.01 (t, 2H, ArH, J = 8.8 Hz), 5.96 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}FN_2O_2$: C, 76.13; H, 3.83; N, 7.10. Found C, 76.02; H, 3.80; N, 7.02.

14-(4-Chlorophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4b). This compound was obtained according to the above general procedure; ir (potassium bromide): 3230, 3184, 3067, 1657, 1635, 1602, 1572, 1468, 1322, 1247, 1089, 780, 617 cm^{-1}; ^{1}Hnmr: δ 10.25 (s, 1H, NH), 8.72-8.73 (m, 1H, ArH), 8.40 (t, 2H, ArH, J = 8.8 Hz), 7.95-8.02 (m, 2H, ArH), 7.66 (t, 1H, ArH, J = 7.6 Hz), 7.43-7.50 (m, 2H, ArH), 7.37-7.40 (m, 3H, ArH), 7.25 (d, 2H, ArH, J = 8.4 Hz), 5.95 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}ClN_2O_2$: C, 73.08; H, 3.68; N, 6.82. Found C, 73.18; H, 3.72; N, 6.89.

14-(4-Bromophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4c). This compound was obtained according to the above general procedure; ir (potassium bromide): 3230, 3019, 2927, 1658, 1635, 1603, 1571, 1468, 1322, 1285, 1087, 778, 617 cm^{-1}; ^{1}Hnmr: δ 10.27 (s, 1H, NH), 8.73-8.74 (m, 1H, ArH), 8.41 (t, 2H, ArH, J = 9.6 Hz), 7.95-8.02 (m, 2H, ArH), 7.67 (t, 1H, ArH, J = 7.6 Hz), 7.44-7.51 (m, 2H, ArH), 7.38-7.41 (m, 3H, ArH), 7.31-7.33 (m, 2H, ArH), 5.94 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}BrN_2O_2$: C, 65.95; H, 3.32; N, 6.15. Found C, 65.90; H, 3.35; N, 6.07.

14-(4-Methoxyphenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4d). This compound was obtained according to the above general procedure; ir (potassium bromide): 3231, 3184, 3014, 1659, 1637, 1605, 1571, 1469, 1321, 1259, 1056, 789 616 cm^{-1}; ^{1}Hnmr: δ 10.21 (s, 1H, NH), 8.71-8.72 (m, 1H, ArH), 8.37-8.44 (m, 2H, ArH), 7.93-8.00 (m, 2H, ArH), 7.65 (t, 1H, ArH, J = 7.6 Hz), 7.43-7.50 (m, 2H, ArH), 7.39 (d, 1H, ArH, J = 8.4 Hz), 7.26 (d, 2H, ArH, J = 8.4 Hz), 6.74 (d, 2H, ArH, J = 8.4 Hz), 5.87 (s, 1H, CH), 3.61 (s, 3H, OCH_3). *Anal.* Calcd for $C_{26}H_{18}N_2O_3$: C, 76.83; H, 4.46; N, 6.89. Found C, 76.89; H, 4.50; N, 6.80.

14-(4-Nitrophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenathrolin-13(14*H*)-one (4e). This compound was obtained according to the above general procedure; ir (potassium bromide): 3228, 3187, 3076, 1661, 1638, 1606, 1578, 1470, 1398, 1252, 1055, 766, 719 cm^{-1}; ^{1}Hnmr: δ 10.38 (s, 1H, NH), 8.73-8.74 (m, 1H, ArH), 8.40-8.46 (m, 2H, ArH), 7.98-8.09 (m, 4H, ArH), 7.65-7.70 (m, 3H, ArH), 7.44-7.52 (m, 2H, ArH), 7.40 (d, 1H, ArH, J = 8.4 Hz), 6.12 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}N_3O_4$: C, 71.25; H, 3.59; N, 9.97. Found C, 71.35; H, 3.63; N, 9.90.

14-(3-Nitrophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenathrolin-13(14*H*)-one (4f). This compound was obtained according to the above general procedure; ir (potassium bromide): 3231, 3138, 3076, 1658, 1635, 1605, 1558, 1468, 1375, 1246, 1056, 757, 615 cm^{-1}; ^{1}Hnmr: δ 10.37 (s, 1H, NH), 8.73 (s, 1H, ArH), 8.48 (d, 1H, ArH, J = 8.4 Hz), 8.41 (d, 1H, ArH, J = 7.6 Hz), 8.21 (s, 1H, ArH), 7.99-8.06 (m, 2H, ArH), 7.95 (d, 1H, ArH, J = 8.4 Hz), 7.83 (d, 1H, ArH, J = 7.2 Hz), 7.67 (t, 1H, ArH, J = 7.6 Hz), 7.44-7.53 (m, 3H, ArH), 7.39 (d, 1H, ArH, J =7.6 Hz), 6.16 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}N_3O_4$: C, 71.25; H, 3.59; N, 9.97. Found C, 71.32; H, 3.64; N, 9.88.

14-(4-Methylphenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4g). This compound was obtained according to the above general procedure; ir (potassium bromide): 3231, 3020, 2921, 1658, 1635, 1603, 1571, 1468, 1376, 1248, 1058, 763, 616 cm^{-1}; ^{1}Hnmr: δ 10.19 (s, 1H, NH), 8.71-8.72 (m, 1H, ArH), 8.37-8.43 (m, 2H, ArH), 7.93-8.00 (m, 2H, ArH), 7.65 (t, 1H, ArH, J = 7.6 Hz), 7.42-7.49 (m, 2H, ArH), 7.38 (d, 1H,

ArH, J = 8.0 Hz), 7.23 (d, 2H, ArH, J = 7.6 Hz), 6.98 (d, 2H, ArH, J = 7.6 Hz), 5.88 (s, 1H, CH), 2.13 (s, 3H, CH_3). *Anal.* Calcd for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found C, 79.90; H, 4.68; N, 7.10.

14-Phenyl-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4h). This compound was obtained according to the above general procedure; ir (potassium bromide): 3226, 3144, 3078, 1657, 1623, 1558, 1470, 1398, 1251, 1061, 923, 833, 753, 617 cm^{-1}; ^{1}Hnmr: δ 10.23 (s, 1H, NH), 8.72-8.73 (m, 1H, ArH), 8.38-8.45 (m, 2H, ArH), 7.95-8.01 (m, 2H, ArH), 7.65 (t, 1H, ArH, J = 8.0 Hz), 7.43-7.50 (m, 2H, ArH), 7.36-7.40 (m, 3H, ArH), 7.19 (t, 2H, ArH, J = 7.6 Hz), 7.07 (t, 1H, ArH, J = 7.2 Hz), 5.93 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{16}N_2O_2$: C, 79.77; H, 4.28; N, 7.44. Found C, 79.70; H, 4.30; N, 7.51.

14-(3,4-Dimethoxyphenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4i). This compound was obtained according to the above general procedure; ir (potassium bromide): 3232, 3066, 2930, 1657, 1635, 1604, 1558, 1418, 1374, 1240, 1058, 912, 762, 611 cm^{-1}; ^{1}Hnmr: δ 10.24 (s, 1H, NH), 8.73-8.74 (m, 1H, ArH), 8.48 (d, 1H, ArH, J = 8.4 Hz), 8.38 (d, 1H, ArH, J = 7.6 Hz), 7.94-8.01 (m, 2H, ArH), 7.66 (t, 1H, ArH, J = 7.6 Hz), 7.44-7.50 (m, 2H, ArH), 7.39 (d, 1H, ArH, J =8.4 Hz), 7.12 (s, 1H, ArH), 6.65-6.73 (m, 2H, ArH), 5.88 (s, 1H, CH), 3.67 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3). *Anal.* Calcd for $C_{27}H_{20}N_2O_4$: C, 74.30; H, 4.62; N, 6.42. Found C, 74.38; H, 4.65; N, 6.49.

14-(2,4-Dichlorophenyl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4j). This compound was obtained according to the above general procedure; ir (potassium bromide): 3228, 3139, 3078, 1656, 1619, 1556, 1470, 1321, 1249, 1088, 965, 885, 757, 613 cm^{-1}; ^{1}Hnmr: δ 10.30 (s, 1H, NH), 8.72-8.73 (m, 1H, ArH), 8.42 (t, 2H, ArH, J = 7.2 Hz), 7.92-8.00 (m, 2H, ArH), 7.67 (t, 1H, ArH, J = 7.6 Hz), 7.46-7.51 (m, 4H, ArH), 7.39 (d, 1H, ArH, J = 8.4 Hz), 7.25 (d, 1H, ArH, J = 8.4 Hz), 6.18 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{14}Cl_2N_2O_2$: C, 67.43; H, 3.17; N, 6.29. Found C, 67.36; H, 3.14; N, 6.36.

14-(Benzo[*d*][1,3]dioxol-6-yl)-7*H*-chromeno[3,4-*b*][4,7]-phenathrnolin-13(14*H*)-one (4k). This compound was obtained according to the above general procedure; ir (potassium bromide): 3232, 3186, 3067, 1659, 1635, 1530, 1469, 1322, 1247, 1099, 946, 852, 616 cm^{-1}; ^{1}Hnmr: δ 10.23 (s, 1H, NH), 8.73-8.74 (m, 1H, ArH), 8.47 (d, 1H, ArH, J = 8.8 Hz), 8.39 (d, 1H, ArH, J = 8.0 Hz), 7.94-8.01 (m, 2H, ArH), 7.66 (t, 1H, ArH, J = 7.6 Hz), 7.45-7.50 (m, 2H, ArH), 7.40 (d, 1H, ArH, J = 8.4 Hz,), 6.94 (s, 1H, ArH), 6.70-6.78 (m, 2H, ArH), 5.88 (s, 1H, CH), 5.86-5.87 (m, 2H, OCH_2O). *Anal.* Calcd for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found C, 74.20; H, 3.88; N, 6.74.

14-(4-Hydroxy-3-nitrophenyl)-7*H*-chromeno[3,4-*b*][4,7]-phenanthrolin-13(14*H*)-one (4l). This compound was obtained according to the above general procedure; ir (potassium bromide): 3326, 3231, 3182, 3070, 1652, 1635, 1533, 1469, 1348, 1229, 1083, 922, 832, 617 cm^{-1}; ^{1}Hnmr: δ 10.82 (s, 1H, OH), 10.31 (s, 1H, NH), 8.74-8.75 (m, 1H, ArH), 8.47 (d, 1H, ArH, J = 8.4 Hz), 8.40 (d, 1H, ArH, J = 8.0 Hz), 7.92-8.04 (m, 2H, ArH), 7.88 (s, 1H, ArH), 7.67 (t, 1H, ArH, J =7.6 Hz,), 7.46-7.51 (m, 3H, ArH), 7.41(d, 1H, ArH, J = 8.4 Hz), 6.94-6.98 (m, 1H, ArH), 5.97 (s, 1H, CH). *Anal.* Calcd for $C_{25}H_{15}N_3O_5$: C, 68.65; H, 3.46; N, 9.61. Found C, 68.60; H, 3.49; N, 9.68.

14-(Thien-2-yl)-7*H*-chromeno[3,4-*b*][4,7]phenanthrolin-13(14*H*)-one (4m). This compound was obtained according to the above general procedure; ir (potassium bromide): 3234, 3143, 3066, 1656, 1636, 1529, 1469, 1321, 1249, 1079, 1051, 832, 617 cm^{-1}; ^{1}Hnmr: δ 10.39 (s, 1H, NH), 8.78-8.79 (m, 1H, ArH), 8.52 (d, 1H, ArH, J = 8.4 Hz), 8.39 (d, 1H, ArH, J = 8.0 Hz), 8.03 (d, 1H, ArH, J = 8.8 Hz), 7.94 (d, 1H, ArH, J = 9.2 Hz), 7.69 (t, 1H, ArH, J = 7.6 Hz), 7.48-7.54 (m, 2H, ArH), 7.44 (d, 1H, ArH, J = 8.0 Hz), 7.20-7.22 (m, 1H, ArH), 6.86-6.87 (m, 1H, ArH), 6.79-6.81 (m, 1H, ArH), 6.29 (s, 1H, CH). *Anal.* Calcd for $C_{23}H_{14}N_2O_2S$: C, 72.23; H, 3.69; N, 7.33; S, 8.38. Found C, 72.31; H, 3.65; N, 7.39; S, 8.30.

Acknowledgements We are grateful to the financial support from the National Natural Science Foundation of China (No. 20672090), the Natural Science Foundation of the Jiangsu Province (No. BK2006033), and Six Kinds of Professional Elite Foundation of the Jiangsu Province (No. 06-A-039).

REFERENCES

[1] (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005; (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004,** 4957; (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; (e) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471; (f) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (g) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (h) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; (i) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

[2] (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*, Blackie Academic & Professional, London, 1998; (c) Lubineau, A.; Auge, J. in *Modern Solvents in Organic Synthesis* (Ed.: Knochel P.), Springer-Verlag, Berlin, Heidelberg, 1999.

[3] (a) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901; (b) Tan, X. H.; Hou, Y. Q.; Huang, C.; Liu, L.; Guo, Q. X. *Tetrahedron* **2004**, *60*, 6129.

[4] (a) Copley, S. D.; Knowles, J. R.; *J. Am. Chem. Soc.* **1987**, *109*, 5008; (b) Khosropour, A. R.; Khodaei, M. M.; Kookhazadeh, M. *Tetrahedron Lett.* **2004**, *45*, 1725.

[5] Dandia, A.; Arya, K.; Sati, M.; Sarawgi, P. *J. Fluorine Chem.* **2004,** *125*, 1273.

[6] Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. T.; Wei, X. Y.; Zong, Z. M. *Tetrahedron Lett.* **2005**, *46*, 7169.

[7] Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747.

[8] Khadilkar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083.

[9] Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811.

[10] Totlani, V. M.; Peterson, D. G. *J. Agric. Food Chem.* **2005**, *53*, 4130.

[11] Wnorowski, A.; Yaylayan, V. A. *J. Agric. Food Chem.* **2000**, *48*, 3549.

[12] Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587.

[13] Hajela, K.; Kapil, R. S. *Eur. J. Med. Chem.* **1997**, *32*, 135.

[14] (a) Horino, H.; Mimura, T.; Kagechika, K.; Ohta, M.; Kubo, H.; Kitagawa, M. *Chem. Pharm. Bull.* **1998**, *46*, 602; (b) Mannhold, R.; Cruciani, G.; Weber, H.; Lemoine, H.; Derix, A.; Weichel, C.; Clementi, M. *J. Med. Chem.* **1999**, *42*, 981; (c) Rovnyak, G. C.; Ahmed, S. Z.; Baird, A. J.; Ding, C. Z.; Dzwonczyk, S.; Ferrata, F. N.; Humphreys, W. G. *J. Med. Chem.* **1997**, *40*, 24.

[15] Sun, H. B.; Chen, W. Y.; Peng, S. X.; Wang, T.; Liu, G. Q. *Gaodeng Xuexiao Huaxue Xuebao* **1997**, *18*, 730; *Chem. Abstr.* **1997**, *127*, 176327.

[16] Kossakowski, J.; Jerzy, Z. T.; Suski, S. *Acta Pol. Pharm.* **1998**, *55*, 77.

[17] El-Shaaer, H. M.; Foltinova, P.; Lacova, M.; Chovancova, J.; Stankovicova, H. *Farmaco* **1998**, *53*, 224.

[18] Johnson, A. T.; Wang, L.; Standeven, A. M.; Escobar, M.; Chandraratna, R. A. S. *Bioorg. Med. Chem.* **1999**, *7*, 1321.

[19] Haas, G.; Jaeggi, K. A.; Rossi, A.; Sele, A. European Patent 13666, 1980; *Chem. Abstr.* **1981**, *94*, 15704.

[20] Hall, C. M.; Wright, J. B.; Johnson, H. G.; Taylor, A. J. *J. Med. Chem.* **1977**, *20*, 1337.

[21] Jastrzebska-Glapa, M., Mlochowski, J.; Sliwa, W. *Pol. J. Chem.* **1979**, *53*, 811.

[22] (a) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J. *Synth. Commun.* **2006**, *36*, 2047; (b) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. *Chem. Lett.* **2005**, *34*, 1316; (c) Pandya, S. U.; Pandya, U. R.; Hirani, B. R.; Brahmbhatt, D. I. *J. Heterocyclic Chem.* **2006**, *43*, 795.

[23] (a) Gusak, K. N.; Tereshko, A. B.; Kozlov, N. G. *Russ. J. Org. Chem.* **2001**, *37*, 1495; (b) Gusak, K. N.; Kozlov, N. G.; Tereshko, A. B. *Russ. J. Org. Chem.* **2004**, *40*, 1322; (c) Kozlov, N. G.; Gusak, K. N.; Tereshko, A. B.; Firgang, S. I.; Shashkov, A. S. *Russ. J. Org. Chem.* **2004**, *40*, 1181; (d) Kadutskii, A. P.; Kozlov, N. G. *Russ. J. Org. Chem.* **2006**, *42*, 1388; (e) Kozlov, N. G.; Pashkovskii, F. S.; Gusak, K. N.; Koroleva, E. V.; Tereshko, A. B.; Lokot, I. P. *Russ. J. Org. Chem.* **2004**, *40*, 555.

[24] Martinez, R.; Cortes, E.; Toscano, R. A.; Alfaro, L. J. *J. Heterocyclic Chem.* **1990**, *27*, 1273.