Microwave-Assisted Aqueous Reactions: An Efficient Route to Benzodiazepines

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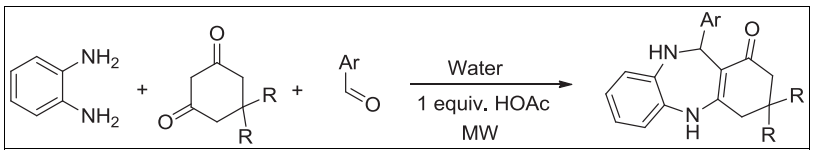

Microwave-assisted three-component reaction has been established for the synthesis of benzodiazepines. This reaction promoted by HOAc was conducted by using readily available and inexpensive starting materials in water under microwave irradiation. The present green synthesis shows fascinating characteristics such as the use of water as the reaction solution, concise one-pot conditions, short reaction periods, easy purification, and reduced waste production without the use of any strong acids or metal promoters.

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INTRODUCTION

Heterocycles containing benzodiazepine rings belong to important building blocks because of their remarkable depressant activity in central nervous system [1] and their being one of the most widely prescribed class of psychotropics [1h–i]. In addition, some of these compounds also possess bioactivities on analgesic, antidepressive, and hypnotic activities [2], and act as neuromedin B receptor antagonists [3a] as well as HCV NS5B polymerase inhibitors [3b]. The remarkable applications of these compounds prompted us to synthesize them. A survey of the literature shows that the majority of the strategies involve either multistep sequences [3–5] or anhydrous conditions [3a], lengthy reaction times [3,4], and laborious workup [3b,4], and is environmentally unfriendly and uneconomical [3,4]. The continuing search for new efficient approaches to benzodiazepine remains a challenge in terms of mild reaction conditions, operational simplicity, economic viability, and eco-friendliness [6].

At the same time, to be a safe, readily available, and environmentally friendly solvent, water has also been recognized as an effective reaction medium with unique properties and possibilities for many organic reactions [7]. There has been growing recognition that water is an attractive medium with unique properties and possibilities for many organic reactions [8]. Multicomponent reactions (MCRs), especially those performed in aqueous medium, have enjoyed a very high prestige in the present synthesis of chemically and biologically important compounds on account of their environmentally friendly atom economy and green characteristics [9–11]. These reactions provide a wide range of possibilities for the efficient construction of a variety of invaluable products in a single operation instead of a tedious multistep synthesis, thus avoiding complicated purifications and saving both solvents and reagents [10]. Therefore, MCRs combined with aqueous media can dramatically reduce the generation of chemical waste and the cost of the starting materials, shorten reaction periods, and giving higher overall chemical yields [12].

In connection with our development of MCRs [12–15], here we would like to report another efficient approach to benzodiazepine that are of chemical and potentially biological importance (Scheme 1). This reaction was conducted by reacting simple 5,5-dimethylcyclohexane-1,3-dione, benzene-1,2-diamines, and aldehydes in water under microwave irradiation without strong acid or any metal catalyst.

RESULTS AND DISCUSSION

We began this study by subjecting 5,5-dimethylcyclohexane-1,3-dione and benzene-1,2-diamine to react with aromatic aldehydes in HOAc or other solvents including EtOH, glycol, DMF, and water in the presence of 1.0 equiv of HOAc under microwave irradiation for condition optimization. As shown in Table 1, the use of glacial acetic acid (HOAc) as a solvent gave product **4a** in 89% chemical yield at 100°C under microwave irradiation. Other organic solvents, such as DMF, EtOH, and glycol

Scheme 1. Three-component synthesis of benzodiazepines.

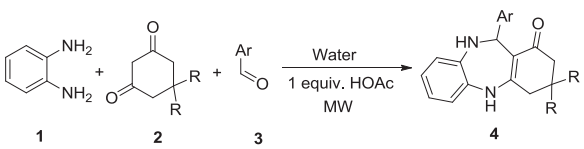
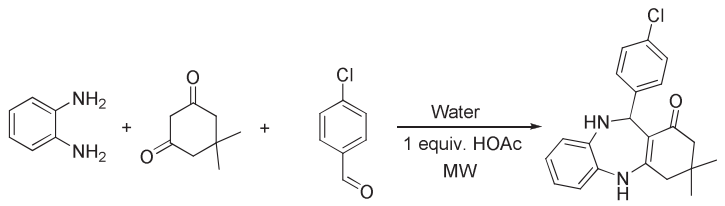


Table 1

Optimizations of reaction conditions under microwave.



Entry	Promoter	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	—	HOAc	100	12	89
2	HOAc (1.0 equiv)	EtOH	100	12	79
3	HOAc (1.0 equiv)	Glycol	100	12	81
4	HOAc (1.0 equiv)	DMF	100	8	75
5	HOAc (1.0 equiv)	Water	100	10	87
6	HOAc (1.0 equiv)	—	100	10	83
7	HOAc (1.0 equiv)	Water	80	15	72
8	HOAc (1.0 equiv)	Water	120	10	86

gave yields of 75–81% at the same temperature promoted by 1.0 equiv of HOAc (entries 2–4), whereas water can achieve a slightly higher yield (87%) when the reaction promoted by 1.0 equiv of HOAc was performed at 100 °C for 10 min under microwave irradiation (entry 5). The same reaction promoted by 1.0 equiv of HOAc was carried out at 100 °C under solvent-free conditions, providing slightly lower yield of **4a** (83%) (entry 6). Water as a good absorber for microwave energy is selected as a reaction solvent in view of its relatively environmentally friendly characteristics [16].

To further optimize the reaction temperature, the identical reaction was carried out at different temperatures ranging from 80 °C to 120 °C. We found that the yield of product **4a** was improved and the reaction time was shortened as the reaction temperature was increased to 100 °C from 80 °C (entry 7). The similar outcome was obtained as the temperature was further increased to 120°C (entry 8).

We then investigated the substrate scope of this synthesis by subjecting a series of aromatic aldehydes **3b–m** to the reactions with **1** and **2a** under the optimal condition. As shown in Table 2, various readily available aromatic

Table 2

The synthesis of compounds **4** under microwave irradiation.[a]

Entry	4	Ar	R	Time (min)	Yield[b] (%)	mp (°C)
1	**4a**	4-ClC_6H_4 (**3a**)	Me (**2a**)	10	87	236–237 (239–240) [5]
2	**4b**	3,4-$Cl_2C_6H_3$ (**3b**)	Me (**2a**)	15	89	138–141
3	**4c**	4-BrC_6H_4 (**3c**)	Me (**2a**)	16	92	245–246 (241–242) [5]
4	**4d**	4-FC_6H_4 (**3d**)	Me (**2a**)	18	87	236–237 (237–239) [5]
5	**4e**	4-$NO_2C_6H_4$ (**3e**)	Me (**2a**)	12	92	271–272 (274–275) [5]
6	**4f**	C_6H_5 (**3f**)	Me (**2a**)	20	84	254–256 (251–252) [5]
7	**4g**	4-$CH_3C_6H_4$ (**3g**)	Me (**2a**)	20	87	232–233
8	**4h**	4-$CH_3OC_6H_4$ (**3h**)	Me (**2a**)	22	85	194–196 (203–205) [5]
9	**4i**	3,4-$(CH_3O)_2C_6H_3$ (**3i**)	Me (**2a**)	22	84	128–129
10	**4j**	2,3-$(CH_3O)_2C_6H_3$ (**3j**)	Me (**2a**)	23	79	236–239
11	**4k**	3,4,5-$(CH_3O)_3C_6H_2$ (**3k**)	Me (**2a**)	24	74	129–131
12	**4l**	4-$N(CH_3)_2C_6H_4$ (**3l**)	Me (**2a**)	24	76	221–222 (228–230) [5]
13	**4m**	2-Thienyl (**3m**)	Me (**2a**)	18	79	240–241
14	**4n**	2-CNC_6H_4 (**3n**)	H (**2b**)	14	85	223–225
15	**4o**	4-$CH_3C_6H_4$ (**3g**)	H (**2b**)	18	87	146–148
16	**4p**	2,3-$(CH_3O)_2C_6H_3$ (**3j**)	H (**2b**)	20	84	223–225
17	**4q**	3,4,5-$(CH_3O)_3C_6H_2$ (**3k**)	H (**2b**)	22	79	130–132

[a]Conditions: the synthesis of products **4**, HOAc (1.0 equiv), water (1.0 mL), 100°C, microwave heating.
[b]Isolated yields.

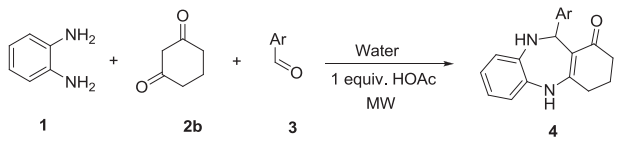
aldehydes bearing either electron-withdrawing or electron-donating functional groups, such as nitro, chloro, bromo, or methyl, were all found to be suitable for the reaction (Table 2, entries 1–13). And after careful analysis, we also observed the delicate electronic effects: aromatic aldehydes with electron-withdrawing groups reacted with a rapid speed, whereas electron-rich groups decreased the reactivity, requiring longer reaction times. Moreover, the reaction of thiophene-2-carbaldehyde with **1** and **2a** was finished within 18 min to give thienyl-substituted benzodiazepines **4m** in 79% yield under this standard condition.

In a further investigation, the scope of the methodology was studied; cyclohexane-1,3-dione was employed instead of 5,5-dimethylcyclohexane-1,3-dione to react with benzene-1,2-diamines and aromatic aldehydes. The reactions occurred rapidly to give the desired products **4n–4q** in 79–87% yields (Scheme 2).

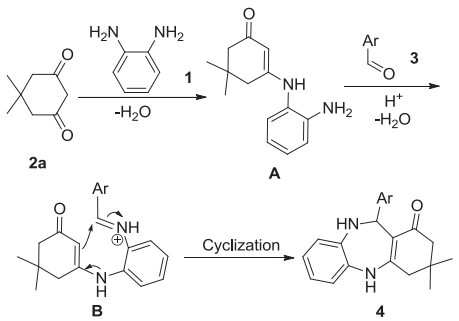
In general, the benzodiazepine of types **4** with molecular versatility and multisubstitutions indicated the efficiency of the three-component one-pot reaction. Furthermore, the functional groups on the framework and the flexible placement of the latent functionalities in these products make them extremely versatile intermediates in further synthetic transformations. The reaction occurred at a very fast speed with all cases finished within 10–24 min. The structures of products **4** have been unambiguously determined by NMR analysis.

On the basis of all the aforementioned results, a plausible mechanism for the reaction was described in Scheme 3. The reaction underwent initial nucleophilic addition and subsequent dehydration to generate intermediate **A**. Then, the intermediate **A** was condensed with aromatic aldehydes to give the intermediate **B**, which is then converted into the final product **4** through intramolecular [6 + 1]cyclization. This type of reaction mechanism is well presented [5,6].

Scheme 2. Three-component synthesis of benzodiazepines.



Scheme 3. Mechanism hypothesis for forming **4**.



In summary, a green and high-efficient approach to benzodiazepine derivatives has been developed by performing the reaction in one-pot fashion in water under microwave irradiation without any metal catalyst. The reactions showed broad substrates of using readily available and inexpensive starting materials of cyclohexane-1,3-dione, benzene-1,2-diamines, and aromatic aldehydes. Particularly, this green synthesis shows several attractive characteristics such as the use of water as the reaction media, simple conditions, short reaction periods, easy work-up, and straightforwardness of the procedure.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator from Biotage Company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on an FTIR Tensor 27 spectrometer (Bruker Company, Ettlingen, Germany) in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer (Bruker Company, Ettlingen, Germany) in DMSO-d_6. The exact mass measurements were obtained by high-resolution mass instrument (Bruker Company, Ettlingen, Germany) (GCT TOF instrument).

General procedure for the synthesis of compounds 4. In a 10-mL reaction vial, a benzene-1,2-diamines **1** (1 mmol), a 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione **2** (1 mmol), HOAc (1 mmol), and water (1 mL) were mixed and stirred within 20 min at room temperature. And then, an aromatic aldehyde **3** (1 mmol) was added into the mixture and capped. The system was subjected to microwave irradiation at 100°C, for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and filtered to give the crude product, which was further washed by 50% EtOH to give pure product **4**. The analytical data of new products are as follows.

11-(3,4-Dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-dibenzo[b,e][1,4]diazepin-1-one (4b). IR (KBr, *v*, cm^{-1}): 3321, 3253, 2957, 2359, 1589; ^1H NMR (DMSO-d_6) (δ, ppm): 8.40 (d, J = 8.4 Hz, 1H, ArH), 7.32(d, J = 1.6 Hz, 1H, ArH), 7.03–7.00 (m, 1H, ArH), 6.97–6.95 (m, 1H, ArH), 6.69–6.60 (m, 2H, ArH), 6.56–6.54 (m, 1H, ArH), 6.27 (d, J = 6.0 Hz, 1H, NH), 5.67 (d, J = 6.0 Hz, 1H, CH), 2.60 (s, 2H, CH_2), 2.20 (d, J = 16.0 Hz, 1H, CH_2), 2.12 (d, J = 16.0 Hz, 1H, CH_2), 1.08 (s, 3H, CH_3), 1.03(s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{21}H_{20}Cl_2N_2NaO$, 409.0846 $[M + Na]^+$; Found: 409.0862.

3,3-Dimethyl-11-p-tolyl-2,3,4,5,10,11-hexahydro-dibenzo[b,e][1,4]diazepin-1-one (4g). IR (KBr, *v*, cm^{-1}): 3305, 2964, 2357, 1584, 1539; ^1H NMR (DMSO-d_6) (δ, ppm): 8.74(s, 1H, NH), 6.99–6.97(m, 2H, ArH), 6.92–6.90(m, 2H, ArH), 6.62–6.51 (m, 3H, ArH), 6.15(d, J = 6.0 Hz, 1H, NH), 5.67 (d, J = 5.6 Hz, 1H, CH), 2.58 (s, 2H, CH_2), 2.20 (d, J = 16.0 Hz, 1H, CH_2), 2.08 (d, J = 16.0 Hz, 1H, CH_2), 2.14 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{22}H_{24}N_2NaO$, 355.1780 $[M + Na]^+$; Found: 355.1792.

11-(3,4-Dimethoxy-phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-dibenzo[b,e][1,4]diazepin-1-one (4i). IR (KBr, *v*, cm^{-1}): 3529, 3284, 2359, 1538; ^1H NMR (DMSO-d_6) (δ, ppm): 8.73(s, 1H, NH), 6.90(d, 1H, J = 8.0 Hz, ArH), 6.84 (d, J = 2.0 Hz, 1H, ArH), 6.64–6.59 (m, 2H, ArH), 6.58–6.54 (m, 2H, ArH), 6.50–6.47 (m,

1H, ArH), 6.13 (d, J = 6.0 Hz, 1H, NH), 5.63 (d, J = 5.6 Hz, 1H, CH), 3.60 (s, 6H, OCH_3), 2.60 (d, J = 16.0 Hz, 1H, CH_2), 2.54 (d, J = 16.0 Hz, 1H, CH_2), 2.22 (d, J = 16.0 Hz, 1H, CH_2), 2.08 (d, J = 16.0 Hz, 1H, CH_2), 1.08 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}N_2NaO$, 401.1835 $[M+Na]^+$; Found: 401.1852.

11-(2,3-Dimethoxy-phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydrodibenzo[b,e][1,4]diazepin-1-one (4j). IR (KBr, ν, cm^{-1}): 3296, 2953, 2358, 1601, 1537; ^1H NMR (DMSO-d_6) (δ, ppm): 8.86 (s, 1H, NH), 6.99–6.97 (m, 1H, ArH), 6.75–6.73 (m, 1H, ArH), 6.67–6.55 (m, 3H, ArH), 6.44–6.42 (m, 1H, ArH), 6.24–6.22 (m, 1H, ArH), 5.99 (d, J = 5.6 Hz, 1H, NH), 5.24 (d, J = 5.6 Hz, 1H, CH), 3.94 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.66 (d, J = 16.0 Hz, 1H, CH_2), 2.58 (d, J = 16.0 Hz, 1H, CH_2), 2.19 (d, J = 16.0 Hz, 1H, CH_2), 2.03 (d, J = 16.4 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.02(s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}N_2NaO$, 401.1835 $[M+Na]^+$; Found: 401.1850.

11-(3,4,5-Trimethoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydrodibenzo[b,e][1,4]diazepin-1-one (4k). IR (KBr, ν, cm^{-1}): 3555, 3306, 2956, 2361, 1587; ^1H NMR (DMSO-d_6) (δ, ppm): 8.78 (s, 1H, NH), 6.93 (d, 1H, J = 8.0 Hz, ArH), 6.66–6.57 (m, 3H, ArH), 6.42(s, 2H, ArH), 6.14 (d, J = 5.6 Hz, 1H, NH), 5.64 (d, J = 6.0 Hz, 1H, CH), 3.59 (s, 6H, OCH_3), 3.53 (s, 3H, OCH_3), 2.64 (d, J = 16.0 Hz, 1H, CH_2), 2.54 (d, J = 16.0 Hz, 1H, CH_2), 2.25 (d, J = 16.4 Hz, 1H, CH_2), 2.09 (d, J = 16.4 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{24}H_{28}N_2NaO_4$, 431.1941 $[M+Na]^+$; Found: 431.1958.

11-(2-Thienyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-dibenzo[b,e][1,4]diazepin-1-one (4m). IR (KBr, ν, cm^{-1}): 3308, 3240, 2949, 1584,1530; ^1H NMR (DMSO-d_6) (δ, ppm): 8.80 (s, 1H, NH), 7.12 (d, J = 5.2 Hz, 1H, ArH), 6.94 (d, J = 7.6 Hz, 1H, ArH), 6.77–6.75 (m, 1H, ArH), 6.70–6.60 (m, 4H, ArH), 6.25 (d, J = 6.0 Hz, 1H, NH), 5.91 (d, J = 5.6 Hz, 1H, CH), 2.60 (d, J = 16.4 Hz, 1H, CH_2), 2.50 (d, J = 16.4 Hz, 1H, CH_2), 2.23 (d, J = 16.0 Hz, 1H, CH_2), 2.09 (d, J = 16.0 Hz, 1H, CH_2), 1.08(s, 3H, CH_3), 1.05(s, 3H, CH_3); HRMS (ESI): *m/z* Calcd for $C_{19}H_{20}N_2NaOS$, 347.1189 $[M+Na]^+$; Found: 347.1199.

2-(1-Oxo-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-11-yl)-benzonitrile (4n). IR (KBr, ν, cm^{-1}): 3387, 3294, 3078, 2954, 2220, 1583; ^1H NMR (DMSO-d_6) (δ, ppm): 9.10 (s, 1H, NH), 7.70 (d, J = 7.2 Hz, 1H, ArH), 7.32–7.29 (m, 1H, ArH), 7.24–7.20 (m, 2H, ArH), 7.07 (d, J = 7.6 Hz, 1H, ArH), 6.86 (d, J = 8.0 Hz, 1H, ArH), 6.72–6.68(m, 1H, ArH), 6.65–6.61 (m, 1H, ArH), 6.52 (d, J = 7.6 Hz, 1H, ArH), 5.95 (d, J = 6.0 Hz, 1H, NH), 5.85 (d, J = 6.0 Hz, 1H, CH), 2.81–2.68 (m, 2H, CH_2), 2.29–2.10 (m, 2H, CH_2), 1.96–1.89 (m, 2H, CH_2); HRMS (ESI): *m/z* Calcd for $C_{20}H_{17}N_3NaO$, 338.1263 $[M+Na]^+$; Found: 338.1274.

11-p-Tolyl-2,3,4,5,10,11-hexahydrodibenzo[b,e][1,4] diazepin-1-one (4o). IR (KBr, ν, cm^{-1}): 3304, 3067, 2945, 2361, 1599; ^1H NMR (DMSO-d_6) (δ, ppm): 8.74(s, 1H, NH), 6.98–6.96 (m, 2H, ArH), 6.90–6.87(m, 3H, ArH), 6.61–6.52 (m, 3H, ArH),6.19(d, J = 6.4 Hz, 1H, NH), 5.67 (d, J = 6.0 Hz, 1H, CH), 2.75–2.62 (m, 2H, CH_2), 2.29–2.19 (m, 2H, CH_2), 2.13 (s, 3H, CH_3) , 1.99–1.88 (m, 2H, CH_2); HRMS (ESI): *m/z* Calcd for $C_{20}H_{20}N_2NaO$, 327.1467 $[M+Na]^+$; Found: 327.1484.

11-(2,3-Dimethoxy-phenyl)-2,3,4,5,10,11-hexahydrodibenzo[b,e][1,4]diazepin-1-one (4p). IR (KBr, ν, cm^{-1}): 3349, 3299, 3240, 3149, 1600, 1535; ^1H NMR (DMSO-d_6) (δ, ppm): 8.88 (s, 1H, NH), 6.97–6.95 (m, 1H, ArH), 6.75–6.72 (m, 1H, ArH), 6.66–6.54 (m, 3H, ArH), 6.43–6.41 (m, 1H, ArH), 6.24–6.22 (m, 1H, ArH), 5.97 (d, J = 5.6 Hz, 1H, NH), 5.22 (d, J = 6 Hz, 1H, CH), 3.93 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.80–2.66 (m, 2H, CH_2), 2.28–2.12 (m, 2H, CH_2), 1.97–1.88 (m, 2H, CH_2); HRMS (ESI): *m/z* Calcd for $C_{21}H_{22}N_2NaO_3$, 373.1522 $[M+Na]^+$; Found: 373.1531.

11-(3,4,5-Trimethoxy-phenyl)-2,3,4,5,10,11-hexahydrodibenzo[b,e][1,4]diazepin-1-one (4q). IR (KBr, ν, cm^{-1}): 3543, 3263, 3064, 2939, 1592, 1531; ^1H NMR (DMSO-d_6) (δ, ppm): 8.79 (s, 1H, NH), 6.91 (d, J = 8.0 Hz, 1H, ArH), 6.66–6.56 (m, 3H, ArH), 6.40 (s, 2H, ArH), 6.17 (d, J = 6.0 Hz, 1H, NH), 5.65 (d, J = 6.0 Hz, 1H, CH), 3.59 (s, 6H, OCH_3), 3.52 (s, 3H, OCH_3), 2.78–2.63 (m, 2H, CH_2), 2.33–2.21 (m, 2H, CH_2), 2.02–1.85 (m, 2H, CH_2); HRMS (ESI): *m/z* Calcd for $C_{22}H_{24}N_2NaO_4$, 403.1628 $[M+Na]^+$; Found: 403.1644.

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REFERENCES AND NOTES

[1] (a) Kumar, R.; Chaudhary, P.; Nimesh, S.; Verma, A. K.; Chandra, R. Green Chem. 2006, 8, 519. (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. Org Lett 2007, 9, 1687. (c) Hart, B. R.; Rush, D. J.; Shea, K. J. J. Am. Chem. Soc. 2000, 122, 460. (d) Shaabani, A.; Maleki, A.; Mofakham, H. J. Comb. Chem. 2008, 10, 595. (e) Murai, K.; Nakatani, R.; Kita, Y.; Fujioka, H. Tetrahedron, 2008, 64, 11034. (f) Ookura, R.; Kito, K.; Ooi, T.; Namikoshi, M.; Kusumi, T. J. Org. Chem. 2008, 73, 4245. (g) Harry, M. G.; Lawrence, L. M.; Charles, A. C.; Frederick, W. D.; Daniel, B. E.; Hansjoerg, K.; Linda, L. S.; Manfred, W. J. Med Chem 1982, 25, 340. (h) Michelini, S.; Cassano, G. B.; Frare, F.; Perugi, G. Pharmacopsychiatry 1996, 29, 127.

[2] (a) Schutz, H. Benzadiazepines, Springer, Heidelberg, 1982; vol. 2, p 240. (b) Smalley R. K., in Comprehensive Organic Chemistry; Barton, D., Ollis, W. D., ed. Pergamon, Oxford, 1979; vol. 4, p 600. (c) Landquist, J. K. in Comprehensive Heterocyclic Chemistry; Katritzk, A. R., Rees, C. W., ed. Pergamon, Oxford, 1984; vol. 1, pp 166–170.

[3] (a) Fu, J.; Shuttleworth, S. J.; Connors, R. V.; Chai, A.; Coward, P. Bioorg Med Chem Lett 2009, 19, 4264. (b) McGowan, D.; Nyanguile, O.; Cummings, M. D.; Vendeville, S.; Vandyck, K.; Van den Broeck, W.; Boutton, C. W.; De Bondt, H.; Quirynen, L.; Amssoms, K; Bonfanti, J. Fr.; Last, S.; Rombauts, K.; Tahri, A.; Hu, L.; Delouvroy, F.; Vermeiren, K.; Vandercruyssen, G.; Van der Helm, L.; Cleiren, E.; Mostmans, W.; Lory, P.; Pille, G.; Van Emelen, K.; Fanning, G.; Pauwels, F.; Lin, T.-I; Simmen, K.; Raboisson, P. Bioorg Med Chem Lett 2009, 19, 2492–2496.

[4] (a) Ukhin, L. Yu.; Suponitskii, K. Yu.; Shepelenko, E. N.; Belousova, L. V.; Orlova, Zh. I.; Borodkin, G. S. Russ. Chem. Bullet. 2011, 60, 1729. (b) Cortéas, E. C.; Baños, M. A.; De Cortés, O. G.-M. J. Heterocyclic Chem., 2004, 41, 277. (c) Cortes, E. C.; Meneses, O. E. A.; Garcia-Mellado, O.; Zuniga, O. C.; Naranjo-Rodriguez, E. B. J. Heterocyclic Chem. 2009, 46, 1113. (d) Tonkikh, N. N.; Strakovs, A.; Rizhanova, K. V.; Petrova, M. V. Chem. Heterocyclic Compounds 2004, 40, 949. (e) Cortes Cortes, E.; Hernandez Sanabria, A. M.; Garcia-Mellado, O. J Heterocyclic Chem 2002, 39, 55. (f) Cortes, E. C.; Cornejo, A. L. V.; de Cortes, G.-M. O. J Heterocyclic Chem 2007, 44, 183.

[5] Kolos, N. N.; Yurchenko, E. N.; Orlov, V. D.; Shishkina, S. V.; Shishkin, O. V. Chem Heterocyclic Compd 2004, 40, 1550.

[6] (a) Bennamane, N.; Kaoua, R.; Hammal, L.; Nedjar-Kolli, B.; Org. Commun. 2008, 1, 62. (b) Pasha, M. A.; Jayashankara, V. P. Indian J. Chem. 2006, 45B, 2716. (c) Vahdat, S.; Baghery M. S. Heteroletters 2012, 2, 43.

[7] (a) Li, C.-J. Chem Rev 2005, 105, 3095. (b) Li, C.-J. Acc Chem Res 2010, 43, 581. (c) Basle, O.; Li, C.-J. Green Chem., 2007, 9, 1047. (d) Li, C.-J.; Chen, L. Chem Soc Rev, 2006, 35, 68. (e) Li, C.-J. Acc Chem Res 2002, 35, 533.

[8] (a) Polshettiwar, V.; Varma, R. S. Chem Soc Rev 2008, 37, 1546. (b) Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press, Oxford, 2000.

[9] (a) Domling, A. Chem Rev 2006, 106, 17. (b) D'Souza D. M.; Muller, T. J. J. Chem Soc Rev 2007, 36, 1095. (c) Tejedor, D.; Garcia-Tellado, F. Chem Soc Rev 2007, 36, 484.

[10] (a) Padwa, A. Chem Soc Rev 2009, 38, 3072. (b) Ganem, B. Acc Chem Res, 2009, 42, 463.

[11] (a) Li, C.-J.; Chen, L. Chem Soc Rev 2006, 35, 68. (b) Li, C.-J. Chem Rev, 2005, 105, 3095. (c) Shore, G.; Yoo, W. J.; Li, C.-J. Organ, M. Chem. Eur. J. 2010, 16, 126.

[12] (a) Terrett, N. K. Combinatorial Chemistry; Oxford University Press: New York, 1998. (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Chem- Eur J 2000, 6, 3321.

[13] (a) Jiang, B; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. J Am Chem Soc 2009, 131, 11660. (b) Jiang, B.; Li, C.; Shi, F.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. J. Org. Chem. 2010, 75, 2962. (c) Jiang, B.; Zhang, G.; Ma, N.; Shi, F.; Tu, S.-J.; Kaur, P.; Li G. Org Biomol Chem 2011, 9, 3834. (d) Jiang, B.; Wang, X.; Shi, F.; Tu, S.-J.; Li, G. Org Biomol Chem 2011, 9, 4025.

[14] (a) Jiang, B.; Wang, X.; Shi, F.; Tu, S.-J.; Li, G. J. Org. Chem. 2009, 74, 9486. (b) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. Green Chem. 2010, 12, 1357. (c) Tu, S.-J.; Cao, X.-D.; Hao, W.-J.; Zhang, X.-H.; Yan, S.; Wu, S.-S.; Han, Z.-G.; Shi, F. Org Biomol Chem 2009, 7, 557. (d) Hao, W.-J.; Jiang, B.; Tu, S.-J.; Cao, X.-D.; Wu, S.-S.; Yan, S.; Zhang, X.-H.; Han, Z.-G.; Shi, F. Org Biomol Chem 2009, 7, 1410. (e) Jiang, B.; Shi, F. and Tu, S.-J. Curr Org Chem 2010, 14, 357–378.

[15] (a) Tu, S.-J.; Zhang, X.-H.; Han, Z.-G.; Cao, X.-D.; Wu, S.-S.; Yan, S.; Hao, W.-J.; Ma, N. J Comb Chem 2009, 11, 428. (b) Jiang, B.; Cao, L.-J.; Tu, S.-J.; Zheng, W.-R.; Yu, H.-Z. J. Comb. Chem. 2009, 11, 612. (c) Jiang, B.; Hao, W.-J.; Wang, X.; Shi, F.; Tu, S.-J. J Comb Chem 2009, 11, 846–850.

[16] (a) Ju, Y.-H.; Rajender, S. V. J. Org. Chem. 2006, 71, 135. (b) Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM Publishing: Mathews, NC, 2002; pp 29–36. (c) Gellis, A.; Boufatah, N.; Vanelle, P. Green Chem. 2006, 8, 483–487. (d) Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563. (e) Arvela, R. K.; Leadbeater, N. E. Org Lett 2005, 7, 2101. (f) Skouta, R.; Varma, R. S.; Li, C. J. Green Chem. 2005, 7, 571. (g) Wu, X.; Larhed, M. Org Lett 2005, 7, 3327–3329.