Highly Diastereoselective Domino Synthesis of 6-Spirosubstituted Pyrido[2,3-*d*]pyrimidine Derivatives in Water

Bo Jiang,[†,‡] Long-Ji Cao,[†] Shu-Jiang Tu,*[,†,‡] Wen-Rui Zheng,[§] and Hai-Zhu Yu[§]

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, Jiangsu, 221116, P. R. China, College of Chemistry, Chemical Engineering, and Materials Science, Suzhou University, Suzhou, P. R. China, and Department of Chemistry, University of Science & Technology of China, Hefei, Anhui, P. R. China

Received March 5, 2009

A highly diastereoselective domino reaction of 2,6-diaminopyrimidine-4-one with structurally diverse aryl aldehydes and various barbituric acids in water under microwave irradiation is described. The products are 6-spiro-substituted pyrido[2,3-*d*]pyrimidines with high diastereoselectivities (up to 99: 1) in which the major diastereomer bears a cis relationship between substituents at the 5- and 7-positions. Furthermore, the mechanism for diastereoselectivity was confirmed by DFT (B3LYP) calculations.

Introduction

Creation of molecular complexity and diversity from simple substrates, with simultaneous consideration of the economic and environmental aspects, constitutes a great challenge in modern organic chemistry, both from academic and industrial points of view. In this context, domino reactions have proven to be very effective and attractive.[1] The notable feature of a domino process is that bonds and new functionalities are constructed during the cascade, which, in turn, react further in subsequent steps under identical conditions to form new bonds and functionalities until termination leads to a stable final product. Clearly, the quality of a domino reaction is dependent on the number of bonds formed and the complexity of the product. The amounts of solvents, reagents, absorbents, and energy in domino reactions would be dramatically decreased compared to the conventional stepwise approach. On the other hand, the multistep synthesis toward a complex compound is laborious and tedious, generating several equivalents of waste and salt as byproduct. Hence, domino processes, in an environmentally benign and atom economic fashion,[2] play an important role in organic synthesis, especially considering that certain complex compounds with high diastereoselectivities, such as 6-spirosubstituted pyrido[2,3-*d*]pyrimidine, are of great significance and their synthesis still remains a challenge for chemists.

Heterocyclic spirocompounds exhibiting structural rigidity because of conformational restriction are of interest in synthetic organic chemistry. Indeed, the presence of a spirocarbon atom induces a relatively large steric strain and allows thermal, base, acid, or photopromoted rearrangement of these products, yielding new and often unexpected heterocycles.[3] Therefore, the synthesis of these spiral structures was of considerable interest in the pharmaceutical and agrocultural chemistry.[4] Recently, synthetic strategies involving diastereoselective domino reactions have manifested themselves as a powerful tool for the rapid introduction and expansion of spirocyclic molecular diversity.[5] Consequently, the design and development of new and highly diastereoselective routes for the generation of spiro heterocycles receives growing interest.[6] However, the utilization of diastereoselective domino reaction to build spirosubstituted pyrido[2,3-*d*]pyrimidine skeleton was seldom investigated.[7] There is only limited number of studies on related spirocyclic system. Quiroga et al.[8] synthesized pyridopyrimidine-spirocyclohexanetriones by treatment of 6-aminopyrimidin-4-ones with dimedone and formaldehyde, but the reactions are not diastereoselective. Wang et al.[9] reported the reaction of *N*-(arylidene)naphthalen-2-amine with arylaldehyde and 1,3-dimethylbarbituric acid to give spiro-benzoquinolines with the disadvantage of poor diastereoselectivity and limited reaction scope. In this paper, we have successfully developed a new domino reaction system to furnish spirosubstituted pyrido[2,3-*d*]pyrimidines with high diastereoselectivity (Scheme 1).

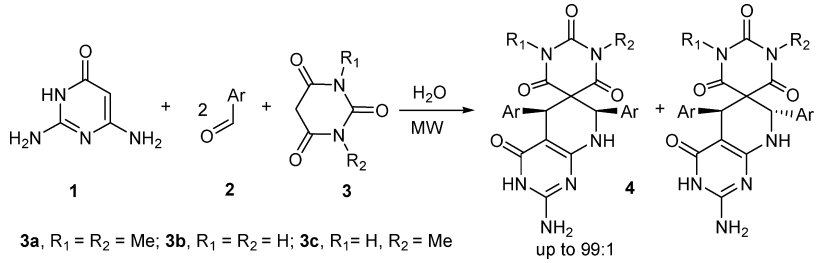
Results and Discussion

In a broad program of developing efficient, selective, and eco-friendly synthetic methods,[10] we started exploring the use of water as reaction media in conjunction with microwave (MW) irradiation as a useful, environmentally benign synthetic treatment.[11] Previous exploration of the reaction of arylaldehydes with 2,6-diaminopyrimidin-4-one and cyclic-1,3-dicarbonyl derivatives proved encouraging because it provided highly functionalized pyrido[2,3-*d*]pyrimidine derivatives and 2,6-diaminopyrimidin-4-one as an efficient reagent displayed high reactivity in water.[12] The significant results led to the further investigation of a new reaction using 2,6-diaminopyrimidin-4-one as starting material. In our initial

* To whom correspondence should be addressed. Phone: 0086-516-83500065. Fax: 0086-516-83500065. E-mail: laotu@xznu.edu.cn.
† Xuzhou Normal University.
‡ Suzhou University.
§ University of Science & Technology of China.

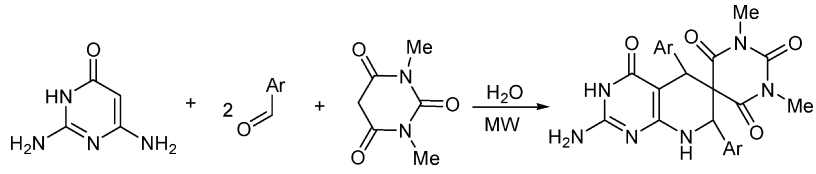
10.1021/cc900038g CCC: $40.75
Published on Web 06/18/2009

Scheme 1. Synthesis of 6-Spirosubstituted Pyrido[2,3-*d*]pyrimidines



3a, $R_1 = R_2 = Me$; **3b**, $R_1 = R_2 = H$; **3c**, $R_1 = H$, $R_2 = Me$

Scheme 2. Optimization of Reaction Conditions for 6-Spirosubstituted Pyrido[2,3-*d*]pyrimidines



Ar = 4-Fluorophenyl

experiment, reaction of 2,6-diaminopyrimidin-4-one **1** with 4-fluorobenzaldehyde **2a** and 1,3-dimethylbarbituric acid **3a** afforded the product in good yield (Scheme 2). The spectroscopic data (^{1}H NMR, ^{13}C NMR) indicated the product was **4a** as a mixture of diastereomers. The structure of the main isomer (*cis*) was unambiguously confirmed by X-ray crystallopraphy (Figure 1).

In an effort to optimize this process, a range of different solvents were investigated. Among various polar solvents tested, glacial acetic acid (HOAc), glycol, and ethanol gave poor to moderate yields of the product **4a** because of the insolubility of diaminopyrimidinone **1**. The best solvent was found to be water. In this solvent, 6-spirosubstituted pyrido[2,3-*d*]pyrimidines (**4a**) was obtained with the best yield. Water is a good absorber for microwave energy[13] and has been successfully employed as a solvent for various organic syntheses;[10g] it turned out to be one of the best choices in view of its relatively environmental-friendly characteristics, as a "cleaner" reaction medium.[10e] With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aryl aldehydes and barbituric acids were investigated (Scheme 2).

At the beginning of the search for the scope in regard to aldehyde, 2,6-diaminopyrimidine-4-one **1** and 1,3-dimethylbarbituric acid **3a** were used as model substrates (Table 1, entries 1−7), and the results indicated that aromatic aldehydes bearing either electron withdrawing or electron donating functional groups such as chloro, fluoro, bromo, methyl or methoxy are suitable for the reaction. Unfortunately, aliphatic aldehydes such as propionaldehyde or butyraldehyde (or heteroaryl aldehyde such as 2-thiophenecarboxaldehyde) produced no product **4**. To expand the scope of barbituric acid substrates, we used different aryl aldehydes and 2,6-diaminopyrimidine-4-one as model substrates and examined various barbituric acid including **3b** and **3c**. In all these cases, reactions proceeded smoothly to give the corresponding 6-spirosubstituted pyrido[2,3-*d*] pyrimidines in excellent yields (Table 1, entries 8−19).

Table 1. Synthesis of 6-spirosubstituted pyrido[2,3-*d*]pyrimidine under MW in Water at 100 °C

entry	Ar	product	R_1	R_2	cis/trans[a]	time/min	yield[b]/%
1	4-fluorophenyl	**4a**	Me	Me	86:14	7	89
2	4-chlorophenyl	**4b**	Me	Me	80:20	7	83
3	4-bromophenyl	**4c**	Me	Me	83:17	6	80
4	phenyl	**4d**	Me	Me	94:6	9	85
5	4-tolyl	**4e**	Me	Me	95:5	8	83
6	4-methoxyphenyl	**4f**	Me	Me	86:14	8	88
7	3,4,5-trimethoxyphenyl	**4g**	Me	Me	>99:1	8	87
8	4-nitrophenyl	**4h**	H	H	92:8	6	81
9	4-fluorophenyl	**4i**	H	H	>99:1	7	90
10	4-bromophenyl	**4j**	H	H	95:5	7	80
11	phenyl	**4k**	H	H	>99:1	7	81
12	3,4,5-trimethoxyphenyl	**4L**	H	H	>99:1	8	86
13	4-methoxyphenyl	**4m**	H	H	93:7	7	89
14	4-bromophenyl	**4n**	Me	H	>99:1	7	83
15	4-fluorophenyl	**4o**	Me	H	93:7	6	89
16	phenyl	**4p**	Me	H	98:2	8	79
17	benzo[*d*][1,3]dioxol-5-yl	**4q**	Me	H	93:7	8	84
18	4-methoxyphenyl	**4r**	Me	H	96:4	8	88
19	4-tolyl	**4s**	Me	H	96:4	8	82

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield of mixtures (cis and trans).

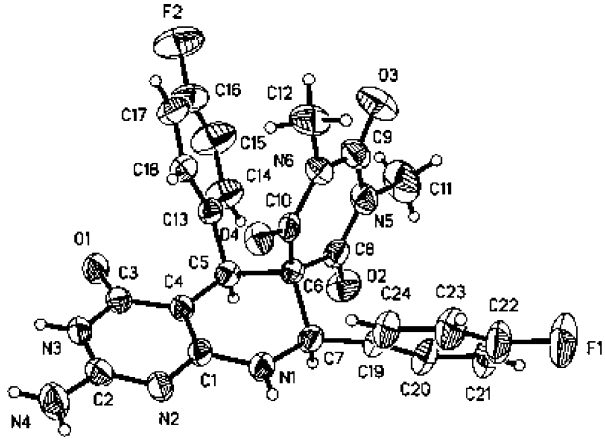
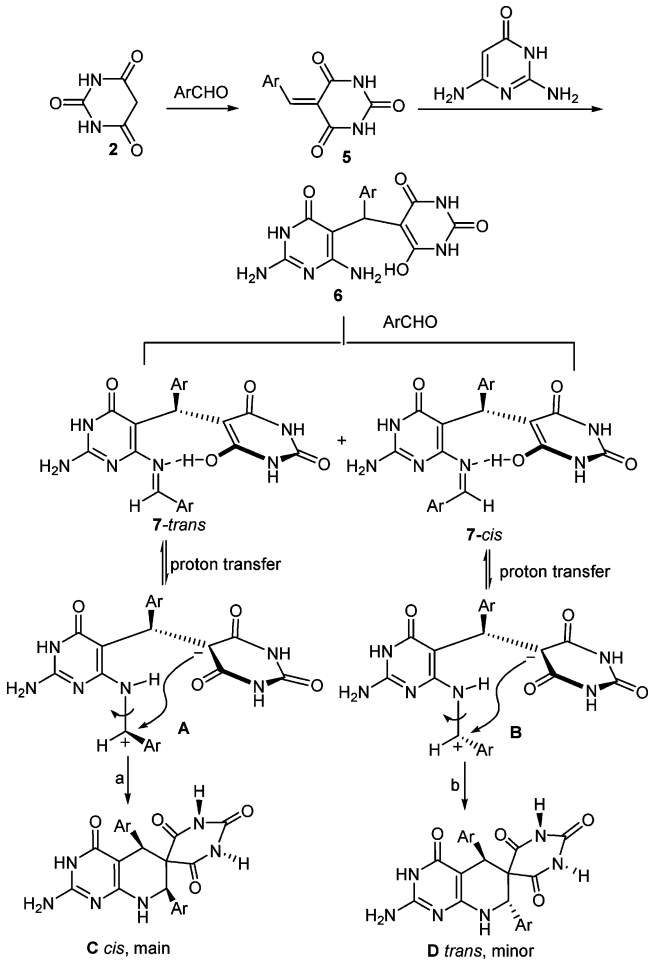


Figure 1. ORTEP drawing of **4a**.

In general, the diastereoselectivity was high, favoring the 5,7-cis disposition of substituents.[14] Stereochemical assignment was made in the case of **4a** in which X-ray data for the cis isomer was obtained (see Supporting Information). Since the chemical shifts of corresponding resonances of the two diastereomers are distinctly different, stereochemical

Scheme 3. Reaction Mechanism of Formation Product **4**



assignment of other compounds prepared was made by analogy with compound **4a** for which conclusive X-ray data was available.

The 6-spirosubstituted pyrido[2,3-*d*]pyrimidine derivatives **4** are likely formed via initial condensation of aromatic aldehyde **2** with barbituric acid **3** to afford the Knoevenagel product **5**, which then undergoes in situ addition reaction with 2,6-diaminopyrimidine-4-one **1** to yield the intermediate product **6** (Scheme 3). Compound **6** further reacted with aldehydes **1** to allow the formation of the aldimines **7** as a mixture of cis- and trans- isomers. The pK_a value of barbituric acid (pK_a = 4.0)[15] is very lower, indicating that proton transfer from the enolized barbituric acid to the imine would be facile. Proton transfer from *trans*- and *cis*-**7** afforded two rotamer zwitterions **A** and **B**, the interconversion of them may be hindered by the intramolecular hydrogen bonding between the amino N−H and the barbituric acid carbonyl group. The rotamer **A** has a trans disposition for the imine's aryl group and the neighboring pyrimidine ring (see Scheme 3) and should be more stable than **B**, where the two groups are cis- to each other to impose significant steric hindrance and repulsive interaction of between aryl group and neighboring pyrimidine ring. This predominance of **A** over **B** before (or during) cyclization produces the thermodynamically more stable cis isomer **C** via path a, whereas the minor trans isomer **D** would result from a similar cyclization from intermediate **B** via path b. The proposed mechanism is similar to Kerr's, which accounts for the cis selectivity in the case

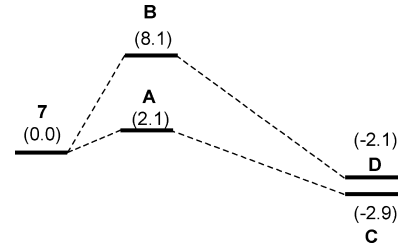


Figure 2. Calculations of the relative energy.

of the aldimines,[16] although we have not been able to separate the aldimines **7** to subject them to the reaction conditions with the goal of probing this hypothesis.

The mechanism for diastereoselectivity was further confirmed by DFT (B3LYP) calculations on the potential intermediates starting from **7** (Scheme 3).[17] Entry 11 was chosen as the model reaction. The relative free energies of these species are shown in Scheme 3. Since the zwitterion intermediate **A** lies only 2.1 kcal/mol higher in the energy than **7**, it is expected that the proton transfer is facial. The energy of rotamer **A** is 6.0 kcal/mol lower than that of **B** and therefore **A** is the main rotamer. An intramolecular nucleophilic attack leads to the cyclization of **A** and **B** to the final products **C** and **D,** respectively. The priority for formation of **C** relative to **D** can be attributed to two factors: first, the predominance of **A** over **B** makes pathway a more plausible than pathway b; second, the cis isomer **C** lies 0.8 kcal/mol lower in the energy than trans isomer **D** (Figure 2). DFT calculations are in good agreement with the experimental results (Table 1) and strongly support the reaction mechanism shown in Scheme 3.

Conclusion

In conclusion, we have reported a novel and highly stereoselective four-component protocol for the domino reactions of 2,6-diaminopyrimidine-4-one with structurally diverse aryl aldehydes and various barbituric acids, resulting in the new production of 6-spirosubstituted pyrido[2,3-*d*]-pyrimidines. These reactions employ microwave heating and water as an environmentally benign reaction medium, and the substrate scope appears to be quite general. This general approach utilized readily available reactants to assemble four new σ bonds including one C−N bond and three C−C bonds in one-pot reactions.

Experimental Section

General. 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. ESI-MS was determined by using the LCQ Advantage HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) was determined by using microTOF-Q|| HRMS/MS instrument (BRUKER).X-ray crystallographic analysis was

performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General Procedure for the Synthesis of Spiro[Pyrido-[2,3-*d*]pyrimidine-6,5′-pyrimidine] Derivatives 4a with Microwave Irradiation (Entry 1, Table 1). In 10-mL vial, 2,6-diaminopyrimidine-4(3*H*)-one (126 mg, 1 mmol), 1,3-dimethylbarbituric acid (156 mg, 1 mmol), 4-fluorobenzaldehyde (248 mg, 2 mmol), and water (2.0 mL) were mixed and then capped. The mixture was irradiated for 7 min at 100 °C (initial power 150 W and maximum power 250 W). Upon completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was filtered, washed with H_2O and EtOH (95%). The solid was purified by recrystallization from DMF/EtOH (v/v = 1:20).

2-Amino-1′,3′-dimethyl-5,7-bis(4-fluorophenyl)-7,8-dihydro-1′*H*,3*H*-spiro[pyrido[2,3-*d*]pyrimidine-6,5′-pyrimidine]-2′,4,4′,6′(3′*H*,5*H*)-tetraone (Entry 1, Table 1): white solid (89% yield); mp >300 °C; IR (KBr, ν, cm^{-1}) 3488, 3388, 3197, 2928, 1747, 1684 cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6, 25 °C, mixture - major isomer only) δ = 9.89 (s, 1H), 7.24 (s, 1H), 7.16−7.12 (m, 4H), 6.93 (t, J = 8.4 Hz, 2H), 6.87−6.83 (m, 2H), 6.14 (s, 2H), 4.88 (s, 1H), 4.71 (s, 1H), 2.90 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ = 169.8, 164.2, 162.5, 160.8, 160.5, 153.6, 149.4, 129.6, 129.5 (2C), 129.4, 115.5, 115.3, 114.3, 114.1, 85.6, 61.5, 60.9, 46.3, 35.9, 31.0, 28.4, 27.5; HRMS *m*/*z* calcd for 495.1587 $[M + H]^+$, found 495.1588 $[M + H]^+$.

Acknowledgment. We are grateful to financial support from the National Science Foundation of China (Nos. 20672090 and 20810102050), Natural Science Foundation of the Jiangsu Province (No. BK2006033), the Qing Lan Project (No. 08QLT001), and Six Kinds of Professional Elite Foundation of the Jiangsu Province (No. 06-A-039). We are grateful to Prof. Qing-Xiang Guo and Dr. Yao Fu from Department of Chemistry University of Science & Technology of China for their helpful discussion.

Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**4s**, DFT (B3LYP) calculations, and crystallographic information files (CIF) of **4a**. This material is available free charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–165. (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (d) Schwier, T.; Sromek, A. W.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868–9878. (e) Barluenga, J.; Jimenez-Aquino, A.; Valdes, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529–1532. (f) Waldmann, H.; Kuhn, M.; Liu, W.; Kumar, K. *Chem. Commun.* **2008**, 1211–1213. (g) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. (h) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(2) (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Diguez-Vzquez, A.; Tzschucke, C. C.; Lam, W. Y.; Le, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 209–212. (c) Muller, F. L.; Constantieux, T.; Rodriguez, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176–17177.

(3) (a) Noheda, M. P.; Tabares, C. N.; Benito, A. R.; Hojas, G. E.; Maroto, S. Q. PCT Int. Appl. WO 2008009695, **2008**; *Chem. Abstr.* **2008**, *148*, 192153. (b) Varma, R. L.; Ganga, V. B.; Suresh, E. *J. Org. Chem.* **2007**, *72*, 1017–1019. (c) Varin, M.; Chiaroni, A.; Lallemand, J.-Y.; Iorga, B.; Guillou, C. *J. Org. Chem.* **2007**, *72*, 6421–6426. (d) Basaric, N.; Marinic, Z.; Sindler-Kulyk, M. *J. Org. Chem.* **2006**, *71*, 9382–9392. (e) Kuethe, J. T.; Varon, J.; Childers, K. G. *Tetrahedron* **2007**, *63*, 11489–11502. (f) Bredenkotter, B.; Florke, U.; Kuck, D. *Chem.—Eur. J.* **2001**, *7*, 3387–3400. (h) Baldwin, J. E.; Shukla, R. *J. Am. Chem. Soc.* **1999**, *121*, 11018–11019. (i) Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D. B.; Sevinle, A. *J. Am. Chem. Soc.* **1989**, *111*, 8466–8470. (j) Bredenkotter, B.; Barth, D.; Kuck, D. *Chem. Commun.* **1999**, 847–848.

(4) (a) Burnett, D. A.; McKittrick, B. A. Int. Patent WO 2008033431, **2008**; *Chem. Abstr.* **2008**, *148*, 369995. (b) Hubschwerlen, C.; Surivet, J.-P.; Zumbrunn, A. C. Int Patent WO 2008026172, **2008**; *Chem. Abstr.* **2008**, *148*, 331358. (c) Sato, T.; Honda, K.; Kawai, T.; Ahn, K. H. *Chem. Abstr.* **2008**, *148*, 215271 WO 2008013280, 2008; (d) Zemolka, S.; Schunk, S.; Bergrath, E.; Koegel, B.-Y.; Englberger, W.; Linz, K.; Schick, H. Int Patent WO 2008009416, **2008**; *Chem. Abstr.* **2008**, *148*, 192112. (e) Balsamo, A.; Calderone, V.; Rapposelli, S. Int Patent WO 2008007210, **2008**; *Chem. Abstr.* **2008**, *148*, 144783. (f) De Micheli, C.; De Amici, M.; Dallanoce, C.; Clementi, F.; Gotti, C. Int Patent WO 2008000469, **2008**; *Chem. Abstr.* **2008**, *148*, 121693. (g) Bursavich, M. G.; Lombardi, S.; Gilbert, A. M. Int Patent WO 2007146138, **2007**; *Chem. Abstr.* **2007**, *148*, 79035. (h) Spyvee, M.; Seletsky, B.; Schiller, S.; Fang, F. Int Patent WO 2007139833, **2007**; *Chem. Abstr.* **2007**, *148*, 33734. (i) Wood, M. R.; Gallicchio, S. N.; Selnick, H. G.; Zartman, C. B.; Bell, I. M.; Stump, C. A. U.S. Patent US 2007265225, **2007**; *Chem. Abstr.* **2007**, *147*, 541857. (j) Gomez-Monterrey, I.; Campiglia, P.; Carotenuto, A.; Califano, D.; Pisano, C.; Vesci, L.; Lama, T.; Bertamino, A.; Sala, M.; Di Bosco, A. M.; Grieco, P.; Novellino, E. *J. Med. Chem.* **2007**, *50*, 1787–1798.

(5) (a) Vellucci, D.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 711–714. (b) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274–2277. (c) Camps, P.; Domingo, L. R.; Formosa, X.; Galdeano, C.; Gonzalez, D.; Munoz-Torrero, D.; Segales, S.; Font-Bardia, M.; Solans, X. *J. Org. Chem.* **2006**, *71*, 3464–3471. (d) Muthusamy, S.; Gunanathan, C.; Nethaji, M. *J. Org. Chem.* **2004**, *69*, 5631–5637.

(6) (a) Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J.-F.; De Santos, J. S.; Metzner, P.; Briere, J.-F. *Org. Lett.* **2007**, *9*, 1745–1748. (b) Muthusamy, S.; Krishnamurthi, J.; Nethaji, M. *Chem. Commun.* **2005**, 3862–3864. (c) Wybrow, R. A. J.; Edwards, A. S.; Stevenson, N. G.; Adams, H.; Johnstone, C.; Harrity, J. P. A. *Tetrahedron* **2004**, *60*, 8869–8880. (d) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719–3722. (e) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543–1546. (f) Aggarwal, V. K.; Barrell, J. K.; Worrall, J. M.; Alexander, R. *J. Org. Chem.* **1998**, *63*, 7128–7129.

(7) Baruah, B.; Bhuyan, P. J. *Tetrahedron lett.* **2009**, *50*, 243–245.

(8) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Tetrahedron lett.* **2006**, *47*, 27–30.

(9) Wang, X.-S.; Zhang, M.-M.; Jiang, H.; Yao, C.-S.; Tu, S.-J. *Chem. Lett.* **2007**, 450–451.

(10) (a) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409–2411. (b) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104. (c) Skouta, R.; Varma, R. S.; Li, C. J. *Green Chem.* **2005**, *7*, 571–575. (d) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329. (e) Ju, Y. H.; Varma, R. S. *J. Org. Chem.* **2006**,

71, 135–141. (f) Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434–1439. (g) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591. (h) Tu, S. J.; Li, C. M.; Li, G. G.; Cao, L. J.; Shao, Q. Q.; Zhou, D. X.; Jiang, B.; Zhou, J. F.; Xia, M. *J. Comb. Chem.* **2007**, *9*, 1144–1148.

(11) (a) Tu, S. J.; Jiang, B.; Zhang, J. Y.; Jia, R. H.; Zhang, Y.; Yao, C. S. *Org. Biomol. Chem.* **2006**, *4*, 3980–3985. (b) Tu, S. J.; Zhang, Y.; Zhang, J. Y.; Jiang, B.; Jia, R. H.; Zhang, J. P.; Ji, S. J. *Synlett* **2006**, 2785–2790. (c) 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*, 1410–1414. (d) 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*, 557–563.

(12) Tu, S. J.; Zhang, Y.; Jiang, H.; Jiang, B.; Zhang, J. Y.; Jia, R. H.; Shi, F. *Eur. J. Org. Chem.* **2007**, 1522–1528.

(13) (a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Mathews, NC, 2002; pp 29−36. (b) Gellis, A.; Boufatah, N.; Vanelle, P. *Green Chem.* **2006**, *8*, 483–487.

(14) (a) Ramachary, D. B.; Barbas III, C. F. *Chem.—Eur. J.* **2004**, *10*, 5323–5331. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233–4237.

(15) (a) Villemin, D.; Labiad, B. *Synth. Commun.* **1990**, *20*, 3207–3212. (b) Villemin, D. *Chem. Ind. (London)* **1983**, 478–479. (c) Villemin, D. *J. Chem. Soc., Chem. Commun.* **1983**, 1092–1093.

(16) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242–8244.

(17) See Supporting Information.

CC900038G