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A Novel Self-Sequence Reaction Network Involving a Set of Six Reactions in One Pot: The Synthesis of Substituted Benzothiazoles from Aromatic Ketones and Anilines

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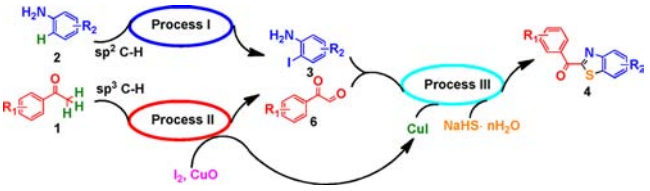
ABSTRACT



Employing simple and readily available aromatic ketones and anilines as starting materials resulted in the construction of 2-acylbenzothiazoles via a novel self-sequence reaction network, which assembles six reactions in one pot. The reaction network not only supplied a novel method for constructing complex molecules but also provided a typical example for logical self-organization synthesis.

The self-organization behavior of molecules is a prominent research topic that has received much attention from scientists.[1] Considering a set of chemical reactions which act on a finite number of molecules in a well-stirred solution, the reaction network is not only a useful vehicle for investigating the self-organization behavior of molecules to imitate biological systems but also an efficient method for the direct construction of complex compounds from simple molecules.[2] As a result, organic synthesis is now evolving away from the manipulation of sets of individual reactions and toward the description and manipulation of systems of reactions.[3] The domino sequence is believed to incorporate a linear domino sequence (Scheme 1A)[3] and multipathway sequence: self-sorting domino sequence (Scheme 1B)[4a] and self-labor domino sequence (Scheme 1C),[4b] etc. However, the convergent integration of two self-labor sequences with a linear domino sequence can be a long-range complex reaction system, which will result in a multipathway reaction network (Scheme 1D), providing a more efficient tool for constructing complex molecules. In this paper, we report a strategy for the synthesis of substituted benzothiazoles via assembling six reactions in one pot.

(1) For selected examples, see: (a) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.* **2009**, *109*, 6275. (b) Camazine, S.; Deneubourg, J. L.; Franks, N. R.; Sneyd, J.; Theraulza, G.; Bonabeau, E. *Self-Organization in Biological Systems*; Princeton University Press: 2003. (c) Vaidya, N.; Manapat, M. L.; Chen, I. A.; Brunet, R. X.; Hayden, E. J.; Lehman, N. *Nature* **2012**, *491*, 72. (d) Schmidt-Mende, L.; Fechtenkötter, A.; Müllen, K.; Moons, E.; Friend, R. H.; Mackenzie, J. D. *Science* **2001**, *293*, 1119.

(2) For selected examples, see: (a) Whitesides, G. M.; Ismagilov, R. F. *Science* **1999**, *284*, 89. (b) Gerdts, C. J.; Sharoyan, D. E.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 6327. (c) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

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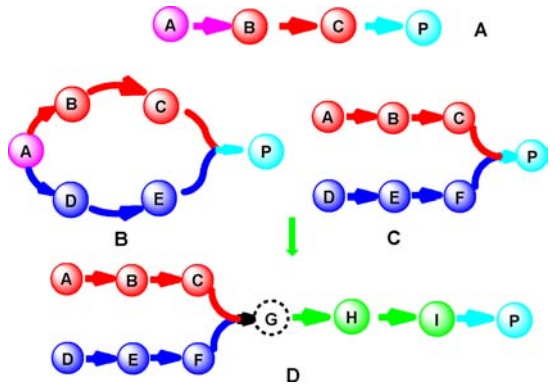
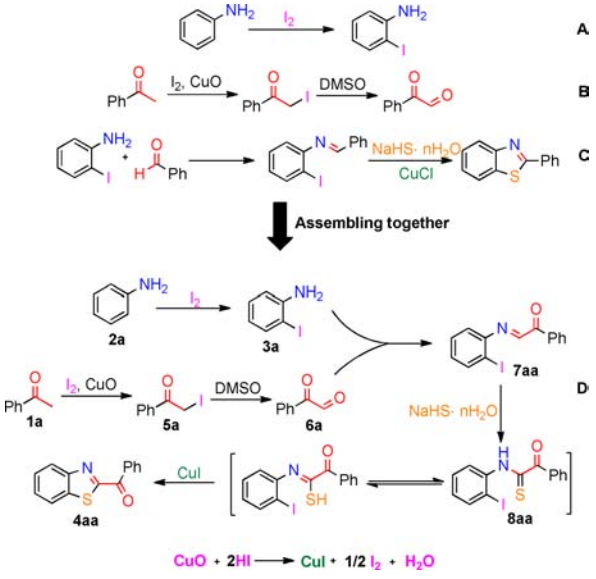
Scheme 1. Integration of the Domino Reactions Strategy



Since benzothiazole is a common building block in biological compounds[5] and functional molecules,[6] an increasing number of studies have been dedicated toward its synthesis. Reported methods have thus far mainly included the directed synthesis[7] and linear domino reaction synthesis[8] of benzothiazole. Herein, two self-labor sequences and a linear domino reaction were bridged to construct benzothiazole via the formation of two C−S bonds and one C−N bond in one pot.

According to previous literatures, aniline can undergo iodidation to afford 2-iodoaniline (Scheme 2A),[9] acetophenone can be sequentially converted to phenylglyoxal (Scheme 2B),[3] and 2-iodoaniline can react with benzaldehyde to generate benzothiazole (Scheme 2C).[8d] On the basis of retrosynthetic analysis, it is suggested that the benzothiazole can be obtained in a novel logical route (Scheme 2D): convergent intergration of two self-labor sequences can be bridged together with a linear domino reaction. We wished that benzothiazole would be generated in a suitable condition through self-sequenced synthesis from readily available starting materials assembling six reactions in one pot.

Scheme 2. Integration of Reactions



To test our hypothesis, acetophenone (**1a**) and 4-methoxyaniline (**2b**) were used as starting compounds to probe the favorable conditions. We found that the target molecule (**4ab**) could be obtained in good yield under the conditions of 1 equiv of **1a**, 1.1 equiv of **2b**, 2 equiv of $NaHS \cdot nH_2O$, 2.5 equiv of iodine, 1 equiv of CuO, 0.5 equiv of Cs_2CO_3, and 0.25 equiv of 1,10-phenanthroline in the presence of a 4 Å molecule sieve in DMSO at 120 °C for 24 h (see Supporting Information).

Based on the successful synthesis of the benzothiazole **4ab** from 4-methoxyaniline **2b**, the optimized conditions were applied to a range of other starting materials. As shown in Scheme 3, generally moderate yields were obtained using aromatic ketones with a substituent (Scheme 3, **4aa** to **4na**). When anilines with an electron-donating substituent in the para-position were used as substrates, the corresponding products were obtained in good yields (Scheme 3, **4ab**, **4ac**, and **4bc**). However, the use of anilines with an electron-withdrawing substituent in the para-position lead to the corresponding products being isolated in low yields or no yield (Scheme 3, **4ad** to **4ag**). It was established that 2-iodoaniline derivatives could not be obtained in good yields with an electron-withdrawing substituent in the para-position (Scheme 3, **4ae** to **4ag**). On the other hand, an electron-donating substituent in the para-position lead to 2-iodoaniline derivatives being generated in good yields (Scheme 3, **4ab**, **4ac**).

To verify that the theoretical model was consistent with the reaction mechanism, several control experiments were performed. When 2-iodoaniline was treated with $NaHS \cdot nH_2O$ in the presence of CuI, aminothiophenol could not be found in the reaction mixture (Scheme 4).[8d] This indicated that the C−S bond of 2-aminobenzenethiol could not form under these conditions.

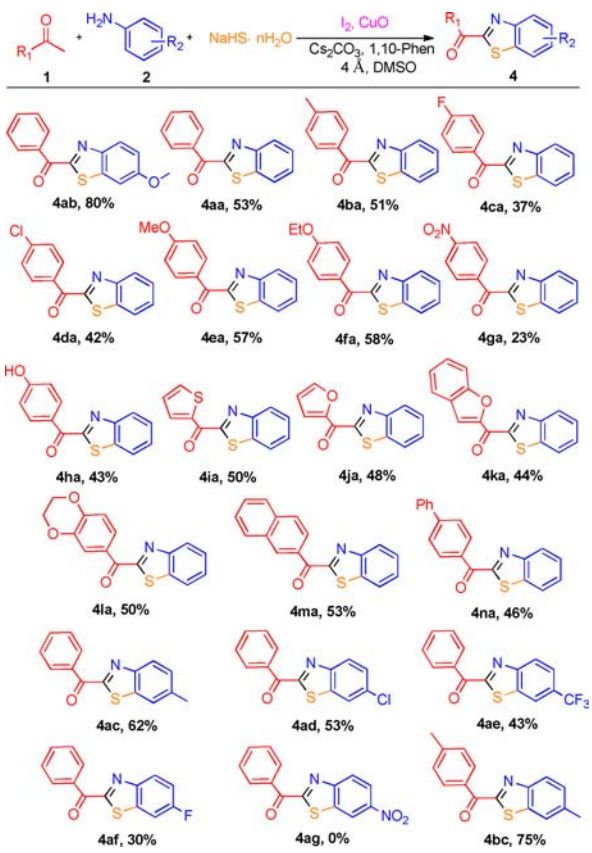
To determine the roles of copper salts in the cyclization reaction, the reactions of phenylglyoxal with 2-iodoaniline and $NaHS \cdot nH_2O$ were carried out under a variety of conditions. The product was not obtained in the absence of CuO and CuI (Scheme 5A). However, when CuI was added to the reaction, the product was formed in 70% yield (Scheme 5B).

(7) For selected examples, see: (a) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Saha, P.; Ramana, T.; Purkati, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (d) Blacker, A. J.; Marsden, S. P.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039. (e) Itoh, T.; Mase, T. *Org. Lett.* **2007**, *9*, 3687. (f) Cheng, Y. Y.; Yang, J.; Qu, Y.; Li, P. X. *Org. Lett.* **2012**, *14*, 98. (g) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147.

(8) For selected examples, see: (a) Mai, D. W.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222. (b) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. (c) Zhu, Y. P.; Lian, M.; Jia, F. C.; Liu, M. C.; Yuan, J. J.; Gao, Q. H.; Wu, A. X. *Chem. Commun.* **2012**, *48*, 9086. (d) Park, N.; Heo, Y.; Kumar, M. R.; Kim, Y.; Song, K. H.; Lee, S. *Eur. J. Org. Chem.* **2012**, *27*, 1984. (e) Ding, Q. P.; Huang, X. G.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 1047. (f) Wang, R.; Chen, Z.; Yue, L.; Pan, W.; Zhao, J. J. *Tetrahedron Lett.* **2012**, *53*, 4529. (g) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. *Org. Lett.* **2009**, *11*, 2039. (h) Sahoo, S. K.; Banerjee, A.; Chakraborty, S.; Patel, B. K. *ACS Catal.* **2012**, *2*, 544. (i) Zhu, Y. P.; Jia, F. C.; Liu, M. C.; Wu, A. X. *Org. Lett.* **2012**, *14*, 4417.

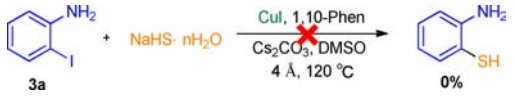
(9) Branytska, O. V.; Neumann, R. *J. Org. Chem.* **2003**, *68*, 9510.

Scheme 3. Synthesis of Benzothiazoles **4** from Aniline **2**[a]

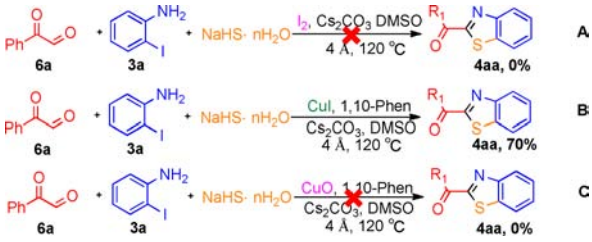


[a] Reaction was performed with 0.5 mmol of **1**, 0.55 mmol of **2**, 1 mmol of NaHS·nH_2O, 1.25 mmol of I_2, and 0.5 mmol of CuO in the presence of a 4 Å molecule sieve, Cs_2CO_3, and 1,10-phenanthroline in 3 mL of DMSO at 120 °C for 24 h. Isolated yields provided.

Scheme 4. Attempted Reaction between **3a** and NaHS·nH_2O



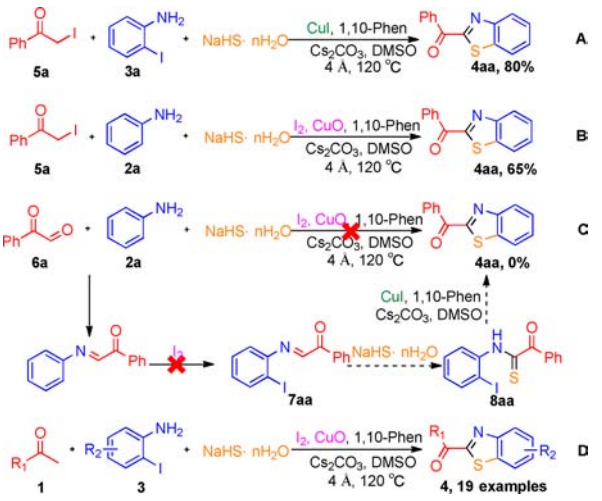
Scheme 5. Effect of Copper in the Reaction



Yet, when CuI was replaced by CuO, the product was not found (Scheme 5C). These results clearly demonstrated that CuI could catalyze the reaction of phenylglyoxal with 2-iodoaniline and NaHS·nH_2O where CuO could not.

In order to prove the reaction mechanism, possible intermediates were isolated and purified to participate in reactions as starting materials (Scheme 6). **5a** was observed to react with **3a** and NaHS·nH_2O to generate **4aa** in good yield in the presence of CuI, Cs_2CO_3, and 1,10-phen (Scheme 6A). The target molecule **4aa** could be obtained from **5a** reacting with **2a** (Scheme 6B). However, **4aa** did not form when **6a** reacted with **2a** (Scheme 6C). This indicated that the intermediate from **6a** reacting with **2a** could not be iodinated to form the target molecule **4aa**. It was subsequently found that benzothiazoles **4** could be obtained from the reaction of aromatic ketones **1** with 2-iodoanilines **3** (Scheme 6D). Capable of assembling five reactions in one pot, this was a novel linear domino reaction: a new method for synthesizing benzothiazoles. All benzothiazole derivates can be obtained in moderate to good yields through this method (19 examples in the Supporting Information).

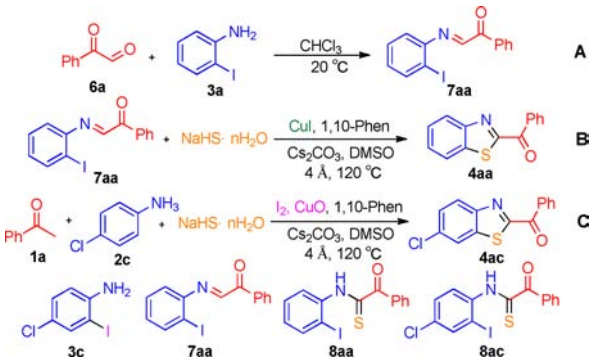
Scheme 6. Reactions between Possible Intermediates



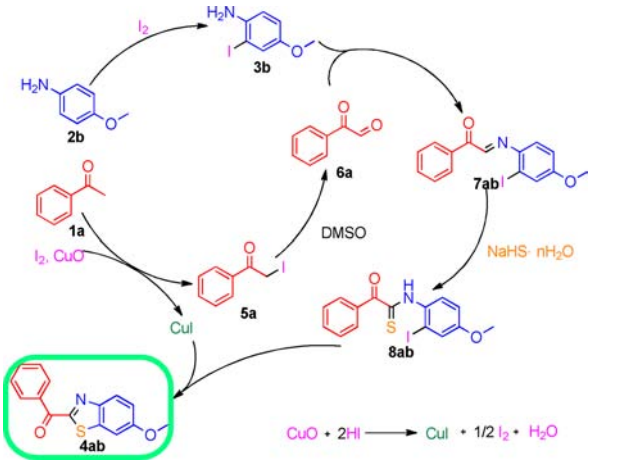
Finally, in order to investigate the detailed reaction process, GC-MS was used to detect the proposed intermediates for this reaction. We could not detect any signals of **7aa**, when **6a** reacted with **3a** in DMSO. This result implied that **7aa** could be oxidized by DMSO. $CHCl_3$ was used as solvent, and **7aa** was subsequently detected in moderate yield (Scheme 7A). Due to the instablility of **7aa**, the crude intermediate **7aa** was used as a substrate to synthesize **4aa**. Fortunately, in addition to the target molecule **4aa**, **8aa** was also be found in the mixture (Scheme 7B). When **1a** and **2c** were used as substrates, **3c** and **8ac** were detected. These results indicated that compounds **3**, **7**, and **8** were important intermediates (Scheme 7C). These experiments implied that the assembling procedure of three sequences in one pot was achieved via the self-organization behavior of the molecule.

Based on the above experiments, we can confirm that the reaction mechanism was consistent with our theoretical model. In addition, the possible mechanism for this reaction can be illustrated with the example of acetophenone

Scheme 7. Detected Reactions by GC-MS



Scheme 8. Plausible Mechanism of the Present Reaction



(**1a**), 4-methoxyaniline (**2b**), and NaHS·nH$_2$O (as shown in Scheme 8). **2b** could be iodinated to **3b**, while acetophenone (**1a**) could be sequentially converted to phenylglyoxal (**6a**) at the same time. Then **3b** could condense with phenylglyoxal (**6a**) to form **7ab**. **7ab** could react with NaHS·nH$_2$O to generate intermediate **8ab**. Based on the literature,[7b] we know that the byproduct CuI could catalyze **8ab** to produce the target molecular **4ab**.

In conclusion, we have achieved the convergent intergration of two self-labor sequences with a linear domino reaction. This novel strategy could be used for constructing benzothiazoles via assembling six reactions in one pot. To the best of our knowledge, this transformation has not only supplied a novel method for directly synthesizing benzothiazoles from readily available aromatic ketones and anilines but has also provided a typical example for self-organization logical synthesis of organic compounds to enrich the reaction network system. Further investigations into the design of new reaction networks and their subsequent applications will be reported in due course.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.