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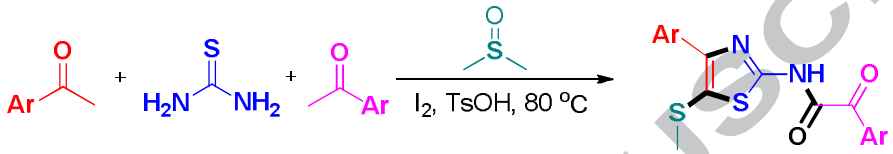

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ABSTRACT

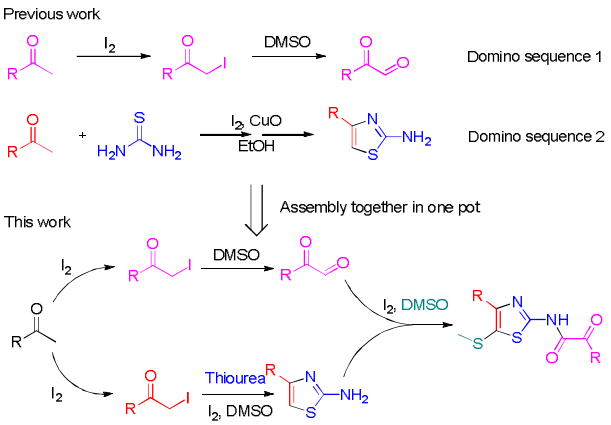
An iodine-promoted selective synthesis has been developed for the construction of subsituted aminothiazole from easily available aryl methyl ketones and thiourea under metal free conditions. This domino process involves the cleavage of C–H, C-O, C-S bonds and the formation of C–N, C-O, C–S bonds.

1. Introduction

One of key challenges in modern organic chemistry lies in the maximisation of synthetic efficiency with the concurrent minimisation of waste.[1] Domino reaction combine a series of chemical processes in a single operation and are thus considered highly economical.[2] Compared with this, however, reaction networks are able to integrate several domino reactions in a well-stirred solution and may thus offer enhanced efficiency in the direct construction of complex compounds from simple molecules.[3] Based on this idea, we focus our attention on the integration of multiple domino sequences to construct reaction network, such as, a self-sorting domino reaction,[4] a focusing domino reaction,[5] and a self-labor domino reaction.[6] In this paper, a novel self-sorting reaction network has been reported for the construction of substituted aminothiazole from simple and readily available starting substrates.

DMSO is a versatile solvent that can be used as an oxidant in Kornblum oxidation[7] or as a reagent in some organic transformations.[8] For example, Qing reported a copper-mediated methylthiolation of aryl C-H bonds, which employed DMSO as a methylthiolation reagent.[8a] In additioin, Cheng and Chen reported a copper-mediated methylthiolation of aryl halides with DMSO.[8b] Kantam also reported a process for the methylthiolation of aryl halides with CuI and $Zn(OAc)_2$, which utilized DMSO as a source of methylthiolation.[8c] Moreover, Yu and coworkers reported a Lewis acid (Ag^I, Ni^{II}, or Fe^{II}) catalyzed, Cu^{II}-mediated thiolation reaction with DMSO as a methylthiolation reagent.[8d] Herein, the reaction utilized DMSO in three important roles: as solvent, oxidant and reagent.

In the previous literature, acetophenone could be sequentially converted to phenylglyoxal via iodination and Kornblum oxidation in the presence of DMSO.[9] In addition, the iodination of acetophenone leads to the formation of phenacyl iodine, which can react with thiourea to form 4-aryl-2-aminothiazoles derivatives.[10] In the current study, the previously reported reactions were integrated for the synthesis of substituted aminothiazole compounds from simple and readily-available aromatic ketones and thiourea (Scheme 1). Moreover, a novel procedure for the methylthiolation of aryl C-H bonds was applied with DMSO as the methylthiolation reagent.



Scheme 1. Integration of two Domino Sequences.

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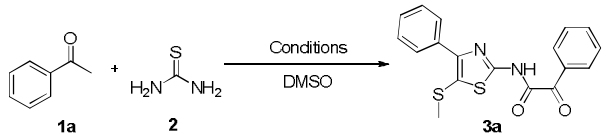
2. Results and discussion

The present study was initiated with acetophenone (**1a**) and thiourea (**2**) as model substrates for the optimization of the reaction conditions. The reaction was screened over a variety of different temperatures, and 80 °C was determined as the optimum temperature (Table 1, entry 3). Various additives were also screened in the reaction, but only TsOH led to a discernible increase in the product yield (Table 1, entry 9). The dosage of iodine was also investigated, but neither increases nor decreases in the dosage were shown to lead to an improved product yield (Table 1, entries 16-19). Based on the results of the aforementioned screening experiments, the optimal reaction conditions were identified as 1 equiv of acetophenone (**1a**), 0.5 equiv. of thiourea (**2**) and 1 equiv of iodine in DMSO at 80 °C (Table 1, entry 9).

Table 1. Optimization of the reaction conditions[a]



1a 2 3a

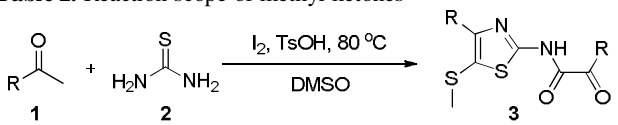
Entry	I_2 (equiv)	Addition (equiv)	Temp (°C)	Yield (%)[b]
1	1.0		40	0
2	1.0		60	12
3	1.0		80	48
4	1.0		100	40
5	1.0		120	28
6	1.0	CuI (0.25)	80	38
7	1.0	CuO (0.25)	80	30
8	1.0	$AlCl_3$ (0.25)	80	22
9	**1.0**	**TsOH (0.25)**	**80**	**55**
10	1.0	AcOH (0.25)	80	21
11	1.0	HCl (0.25)	80	10
12	1.0	$CsCO_3$ (0.25)	80	11
13	1.0	Na_2CO_3 (0.25)	80	12
14	1.0	K_2CO_3 (0.25)	80	10
15	1.0	DBU(0.25)	80	11
16		TsOH (0.25)	80	0
17	0.5	TsOH (0.25)	80	38
18	1.5	TsOH (0.25)	80	41
19	2.0	TsOH (0.25)	80	40

[a] Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol) in 3 mL DMSO for 12 h.

[b] Isolated yields.

With the optimal reaction conditions in hand, the scope and generality of this procedure was subsequently examined using a range of aryl methyl ketones (Table 2). The reaction was successfully applied to a range of substituted aromatic ketones, with the corresponding products being formed in moderate yields. Aromatic ketones bearing electron-donating groups (e.g., 4-Me, 4-OMe, and 4-OEt) reacted smoothly under the optimized conditions to provide the corresponding products **3b-d** in moderate yields (40–58%, Table 2). Slightly lower yields were obtained when the optimized conditions were applied to aromatic ketones bearing electron-withdrawing halogen groups (e.g., 4-F, 4-Cl, and 4-Br), with the corresponding products **3e-g** obtained in moderate yields (50–54%, Table 2). Furthermore, 2-naphthyl-methyl ketone (**1h**) was also seen to react smoothly under the optimized conditions to give the aminothiazole product (**3h**) in moderate yield (43%, Table 2). However, 4-Nitroacetophenone was found unable to react under the standard conditions (Table 2, **3i**), which suggested that the strong electron-withdrawing groups at the *para* position of the aromatic ketone had an adverse impact on the reaction. No target molecule could be found when 1-methylthiourea and 1-phenylthiourea were used as starting material in the reaction. The structure of the product was further confirmed by an X-ray crystallographic study of **3a** (Fig. 1).[11]

Table 2. Reaction scope of methyl ketones[a]



1 2 3

Entry	**1** (R)	**3**	Yields[b] (%)
1	**1a** (C_6H_5)	**3a**	55
2	**1b** (4-MeC_6H_4)	**3b**	58
3	**1c** (4-$MeOC_6H_4$)	**3c**	42
4	**1d** (4-$EtOC_6H_4$)	**3d**	40
5	**1e** (4-FC_6H_4)	**3e**	54
6	**1f** (4-ClC_6H_4)	**3f**	50
7	**1g** (4-BrC_6H_4)	**3g**	53
8	**1h** (2-Naphthyl)	**3h**	43
9	**1i** (4-NO_2-C_6H_4)	**3i**	0

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), TsOH (0.25 mmol) and I_2 (1.0 mmol) in DMSO (3 mL) at 80 °C for 12 h.

[b] Isolated yields.

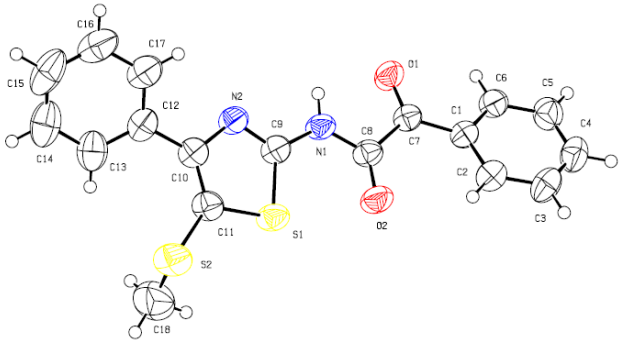
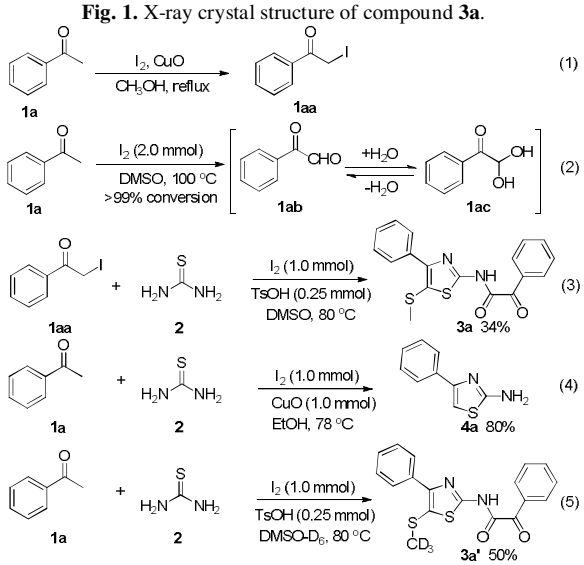


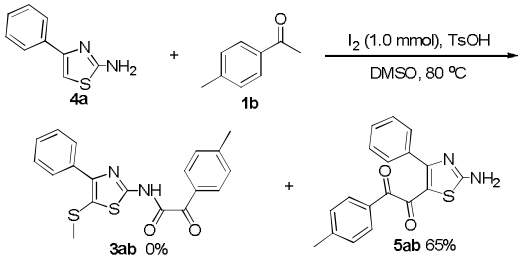
Fig. 1. X-ray crystal structure of compound **3a**.



Scheme 2. The controlled experiments to prove the mechanism.

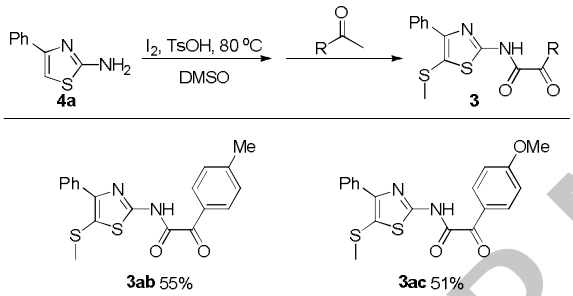
To gain some insights into the mechanism of the reaction, a series of control experiments were performed. Acetophenone (**1a**) was converted into α-iodo acetophenone (**1aa**) in 96% yield using the I_2/CuO system (Scheme 2 (1)). When acetophenone **1a** was heated with I_2 in DMSO at 100 °C in the absence of thiourea (**2**), the substrate was transformed into phenylglyoxal (**1ab**) or hydrated hemiacetal (**1ac**) in quantitative conversion (Scheme 2 (2)). The target molecule (**3a**) could also be obtained from the

reaction between α-iodo acetophenone (**1aa**) and thiourea (**2**) (Scheme 2 (3)). Moreover, intermediate 2-aminothiozole (**4a**) could be obtained from acetophenone (**1a**) and thiourea (**2**) in EtOH at 78 °C (Scheme 2 (4)). Furthermore, DMSO-D_6 was subjected to the transformation and the target molecule (**3a'**) was obtained (Scheme 2 (5)), which indicated that the methylthio in **3** originated from DMSO.



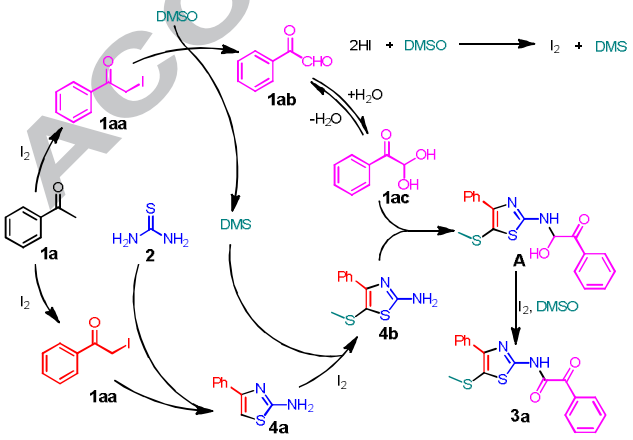
Scheme 3. The controlled experiment to prove the mechanism.

Subsequently, 2-aminothiozole (**4a**) was used as a starting material to react with 4'-methylacetophenone (**1b**) to form the target molecule (Scheme 3). However, the product (**3ab**) could not be obtained and the byproduct **5ab** was separated, which indicated that the 5-position of thiazole was more likely to react with aryl methyl ketones than the amino of aminothiazole.



Scheme 4. The step by step experiment for the addition of aryl methyl ketones.

The proposed mechanism was further verified through a step by step examination of the addition process of intermediate 2-aminothiozole (**4a**) and aryl methyl ketones under the standard conditions (Scheme 4). Intermediate 2-aminothiozole (**4a**) was added in the vessel under the standard conditions for 4h. The target molecules were then obtained following the addition of various aryl methyl ketones. This confirmed that the 5-position of thiazole was more likely to react with aryl methyl ketones than the amino of aminothiazole.



Scheme 5. The plausible mechanism of the present reaction.

Based on the aforementioned results and previous reports, a plausible mechanism for the current reaction was proposed as follows with acetophenone (**1a**) as an example (Scheme 5). Initially, substrate **1a** was converted into the intermediate α-iodo acetophenone (**1aa**) in the presence of I_2. Subsequently, the oxidation of intermediate **1aa** by DMSO occurred to yield intermediate phenylglyoxal (**1ab**) or hydrated hemiacetal **1ac**. Meanwhile, α-iodo acetophenone (**1aa**) reacted with thiourea (**2**) to generate intermediate 2-aminothiozole (**4a**). Intermediate **4a** could then be converted to **4b** in the presence of I_2 and DMS.[4] The reaction of hydrated hemiacetal **1ac** with thiourea (**2**) afforded intermediate **A**, which subsequently underwent a Kornblum oxidation reaction to generate the desired product **3a**. In the process, the byproduct HI was oxidized by DMSO to regenerate at least 0.5 equiv of iodine.[9]

3. Conclusion

In conclusion, this work has proposed an iodine-promoted self-sorting reaction network for the construction of aminothiazole derivatives from readily-available methyl ketones and thiourea. Notably, this metal-free transformation generated five new bonds including two C-N bonds, one C-O bond and two C-S bonds. Further studies towards the applications of this reaction will be reported in due course.

Acknowledgments

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References and notes

1. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Sheldon R. A. *Pure Appl. Chem.* **2000**, *72*, 1233; (c) Anastas P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301; (d) Cao, J. J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976; (e) Zhu, Y. P.; Gao, Q. H.; Lian, M.; Yuan, J. J.; Liu, M. C.; Zhao, Q.; Wu, A. X. *Chem. Commun.* **2011**, *47*, 12700.
2. For selected examples, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2006; (b) Zhu, J. P.; Bienaymé, H. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
3. 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.
4. Yin, G. D.; Zhou, B. H.; Meng, X. G.; Wu, A. X.; Pan, Y. J. *Org. Lett.* **2006**, *8*, 2245.
5. Gao, M.; Yang, Y.; Wu, Y. D.; Deng, C.; Cao, L. P.; Meng, X. G.; Wu, A. X. *Org. Lett.* **2010**, *12*, 1856.
6. Xue, W. J.; Li, Q.; Zhu, Y. P.; Wang, J. G.; Wu, A. X. *Chem. Commun.* **2012**, *48*, 3485.
7. For selected examples, see: (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562; (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113; (c) Paquette, W. D.; Taylor, R. E. *Org. Lett.* **2004**, *6*, 103.
8. (a) Chu, L.; Yue, X.; Qing, F. L. *Org. Lett.* **2010**, *12*, 1644; (b) Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304; (c) Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Sreedhar, B. *Tetrahedron* **2013**, *69*, 8276; (d) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y. F. *J. Org. Chem.* **2012**, *77*, 4414.
9. Gao, M.; Yang, Y.; Wu, Y. D.; Deng, C.; Shu, W. M.; Zhang, D. X.; Cao, L. P.; She, N. F.; Wu, A. X. *Org. Lett.* **2010**, *12*, 4026.
10. Zhu, Y. P.; Yuan, J. J.; Zhao, Q.; Lian, M.; Gao, Q. H.; Liu, M. C.; Yang, Y.; Wu, A. X. *Tetrahedron* **2012**, *68*, 173.
11. The details of the crystal data have been deposited with CambridgeCrystallographic Data Centre as Supplementary Publication, CCDC995977.

Supplementary Material

Evidence in support of the hypothetic mechanism, and ^{1}H and ^{13}C NMR spectra and X-ray crystal data for **3a**. Supplementary data related to this article can be found online at doi:

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