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# Ultrasound irradiation promoted catalyst-free construction of formamidine framework using isocyanide as building blocks

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ABSTRACT

Reactions of isocyanides with 2-mercaptobenzothiazole and 2-mercaptobenzoxazole afforded a series of compounds containing formamidine framework in moderate to high yields. These organic transformations were performed under mild and catalyst-free conditions. In addition to promoting the reactions, the use of ultrasound irradiation also allowed the process to be carried out under air atmosphere. A possible reaction mechanism was proposed based on the experimental results.



Formamidine, as one of the most important nitrogen-containing compounds, has attracted more and more research interest since its synthetic utility was firstly studied by Meyers and Hoeve.[1] Later on, wide application of formamidines in organic synthesis,[2] biochemistry,[3] and coordination chemistry[4] had been discovered. It was also a key motif in many bio-active molecules such as pesticide.[5] In view of the requirement for insightful understanding of the properties and applications of formamidine derivatives, the synthetic methodology of which had been another focus of research. Three main methods established in an early period for the synthesis of formamidines had been summarized by Du,[6] which include combinatorial synthesis of DMF-DMA-primary amine, DMF-dimethyl sulfate-primary amine, and metathesis between formamidines and secondary amines. Nevertheless, a highly efficient method with wider generality of substrates for the synthesis of functional molecules with structural diversity and complexity is still desirable.

Reaction based on the isocyanide building blocks has been demonstrated to be a convenient access to compounds with structural diversity and complexity since the midst of last century,[7] which promoted us to direct our research interest toward isocyanide-based reaction chemistry. During the course of extending our findings to the synthesis of heterocycles (Scheme 1, Eq. 1),[8] we unexpectedly found that the reaction of *tert*-butyl isocyanide, 2-mercaptobenzothiazole, and *gem*-dicyano olefin generated a formamidine derivative (Scheme 1, Eq. 2). On the basis of this result, we can see that the *gem*-dicyano olefin did not participate in the reaction, which may be due to the steric hindrance of the olefin acceptor. The formation of the formamidine framework obviously indicated the insertion of *tert*-butyl isocyanide into N–H bond occurred. The [S═CNC═N(*t*Bu)] backbone in the product is very similar to the β-ketiminate ligand, and the latter has found significant applications in coordination chemistry and organometallic catalysis.[9] Compared to the harsh and strong acidic conditions which are often required in the synthesis of β-ketiminate ligand, the neutral and mild conditions demonstrated in our case were superior in constructing such scaffold. In view of this, we repeated the reaction without the use of the *gem*-dicyano olefin (Scheme 2), the same result was obtained eventually. Inspired by this interesting result, we focused our attention on the synthesis of various formamidine derivatives.

Interaction of isocyanide with compound containing active N–H bond, as an eco-friendly method for the construction of formamidine scaffold, has previously been established by Saegusa et al. via group IB and IIB metal-catalysis.[10] However, the use of high catalyst loading (>20 mol %) and elevated reaction temperature made the procedure less efficient and economical. Chupp's group firstly disclosed the reaction of isocyanide with heterocyclic amide/thioamide such as benzimidazoline-2-thione under catalyst-free condition.[11] However, some limitations such as low to moderate yields, the complicated workup for each reaction as well as the requirement of inert gas atmosphere hindered its wide application in organic synthesis. Based on the limitations from previous contributions as well as the new result we obtained above, herein we describe an efficient method for the construction of formamidine scaffold under mild and catalyst-free conditions.

The reaction of *tert*-butyl isocyanide **2a** with 2-mercaptobenzothiazole **1a** in the mixture of MeCN and $H_2O$ was selected as a template for the optimization of reaction conditions. In our earlier

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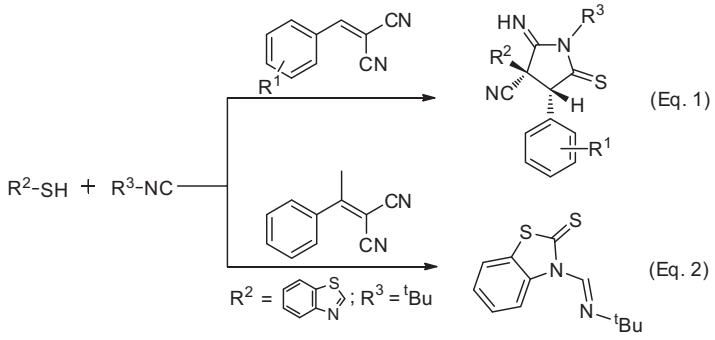
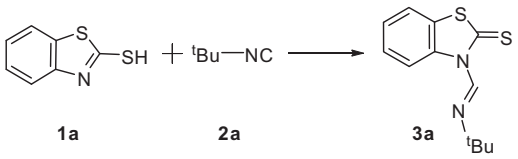


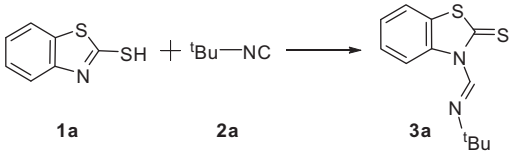

**Scheme 1.**




**Scheme 2.**

work, water was found to have an acceleration effect on the synthesis of imino-pyrrolidine-thione.[8] However, in the present case, this positive effect hasn't been exhibited via a high-throughput screening. Thus, acetonitrile was used as the sole solvent for the further study. The influence of solvent-volume on the reaction was firstly explored. As can be seen from Table 1, under traditional stirring condition at room temperature, varying the volume of sol-

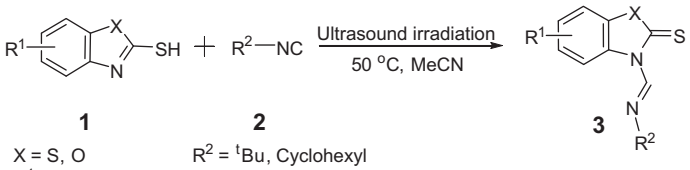
**Table 1**
Optimization of reaction condition[a]




| Entry | Solvent | $V_{sol}$[b] (mL) | T (°C) | Reaction condition[c] | Yield[d] (%) |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 1.0 | rt | A | 28 |
| 2 | $CH_3CN$ | 0.5 | rt | A | 31 |
| 3 | $CH_3CN$ | 0.1 | rt | A | 33 |
| 4 | $CH_3CN$ | 1.0 | 50 | B | 48 |
| 5 | $CH_3CN$ | 1.0 | Reflux | B | Messy |
| 6 | $CH_3CN$ | 1.0 | 50 | C | 61 |
| 7 | $CH_3CN$ | 0.5 | 50 | C | 75 |
| **8** | **$CH_3CN$** | **0.1** | **50** | **C** | **83** |
| 9 | EtOH | 0.1 | 50 | C | 59 |
| 10 | MeOH | 0.1 | 50 | C | 51 |
| 11 | PhMe | 0.1 | 50 | C | 77 |
| 12 | $CH_2Cl_2$ | 0.1 | 50 | C | 53 |
| 13 | $CHCl_3$ | 0.1 | 50 | C | 75 |
| 14 | $Et_2O$ | 0.1 | 50 | C | 73 |
| 15 | THF | 0.1 | 50 | C | 72 |
| 16 | 1,4-Dioxane | 0.1 | 50 | C | 65 |
| 17 | $CH_3NO_2$ | 0.1 | 50 | C | 70 |
| 18 | DMF | 0.1 | 50 | C | 80 |

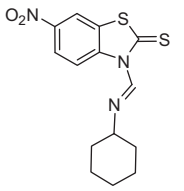
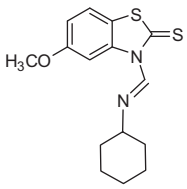
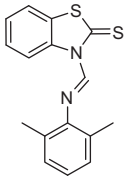
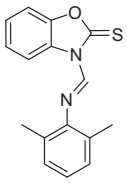
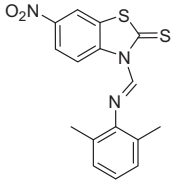
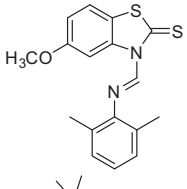
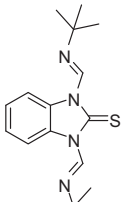
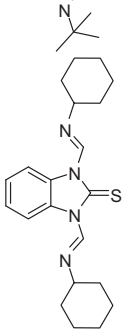
[a] All the reactions were performed for 6 h.
[b] Volume of solvent.
[c] A: conventional stirring; B: conventional heating and stirring; C: ultrasonic irradiation.
[d] Isolated yield.

**Table 2**
Substrate scope study[a]




| Entry | Product | | Time (h) | Yield[b] (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | | **3a** | 6 | 83 | 105–106 |
| 2 | | **3b** | 28 | 73 | 144–146 |
| 3 | | **3c** | 22 | 93 | 245–248 |
| 4 | | **3d** | 22 | 75 | 115–118 |
| 5 | | **3e** | 22 | 76 | 131–133 (131–132)[c] |
| 6 | | **3f** | 22 | 91 | 105–107 |

**Table 2** (*continued*)

| Entry | Product | | Time (h) | Yield[b] (%) | Mp (°C) |
|---|---|---|---|---|---|
| 7 |  | **3g** | 22 | 95 | 242–244 |
| 8 |  | **3h** | 22 | 74 | 108–110 |
| 9 |  | **3i** | 12 | 85 | 151–153 (150–151) [c] |
| 10 |  | **3j** | 12 | 69 | 166–167 (167–168) [c] |
| 11 |  | **3k** | 12 | 92 | 292–294 (>290)[c] |
| 12 |  | **3l** | 12 | 71 | 158–159 |
| 13 |  | **3m** | 16 | 34 | 164.1–164.4 |
| 14 |  | **3n** | 20 | 21 | 211.1–212.0 |

[a] Reaction condition: **1** (0.5 mmol), **2** (0.5 mmol), 0.1 (or 0.2 mL) MeCN, ultrasonic irradiation at 50 °C.
[b] Isolated yield.
[c] See Ref. 9.

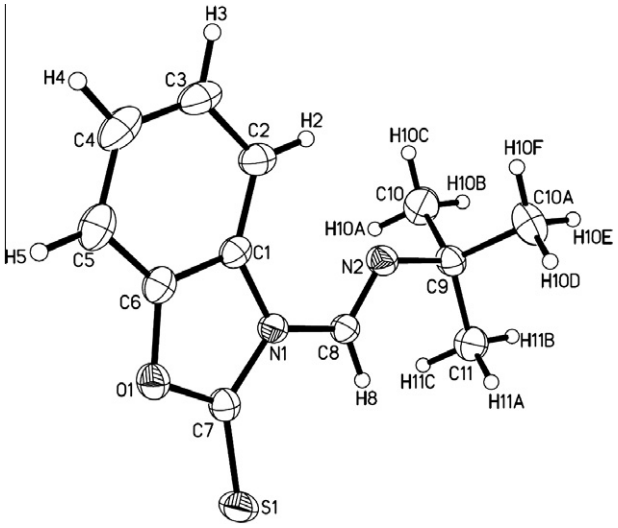
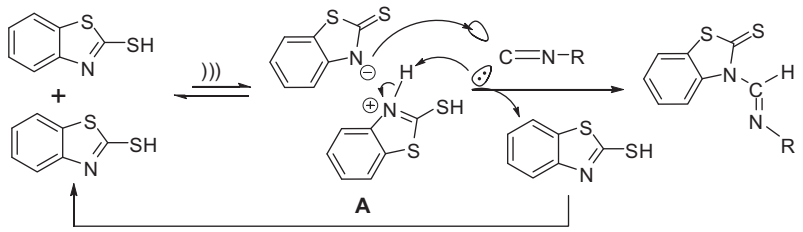



**Figure 1.** Crystal structure of compound **3b**.

vent from 1 to 0.1 mL led to only a little increase of product yield (entries 1–3). So we tested the reaction at a higher temperature. We were delighted to find that the desired product **3a** could be obtained in 48% yield when the reaction was performed at 50 °C. However, performing the reaction at even higher temperature made the reaction messy (entries 4 and 5), which may be due to the fact that I-MCR is often highly inert atmosphere-dependant at high temperature.[12] Thus, a more efficient procedure that can be carried out under relatively mild reaction conditions becomes desirable. With the devolopment of new synthetic technology in organic chemistry, ultrasound irradiation has been considered as a clean and efficient technique for organic synthesis during the last three decades.[13] In general, sonication increases reaction rates and yields without using harsh conditions, and we also have realized a few organic transformations by using this promising technique.[14] Taking these advantages into account, we carried out the above reaction under ultrasound irradiation condition at 50 °C. As expected, the template reaction could proceed smoothly to afford the desired product **3a** in 61% yield (entry 6). In addition, it was found that a decrease of the volume of solvent led to an increase of product yield to 83% (entries 7 and 8). Morever, it should be noted that the use of ultrasound irradiation also allowed the template reaction to be performed without the protection of inert atmosphere. The effect of solvent on the reaction was also investigated under ultrasound irradiation condition. As is shown in entries 9–18, the model reaction can proceed well in all the solvents screened such as alcohol, DMF, and ethers. Among them, the best result (83% yield, entry 8) was obtained when MeCN was used as solvent. In the meantime, the addition of other metal catalyst ($ZnCl_2$ or CuCl) showed no acceleration for the reaction rate.

After the optimal reaction conditions were established, we continued to explore the generality of the protocol.[15] The outcome was listed in Table 2. We could clearly see that when 2-mercaptobenzothiazoles with either electron-donating substituent or electron-withdrawing group were introduced, the reactions also worked well leading to moderate to high yields of the desired products (entries 3, 4, 7, 8, 11, and 12).

Compared to 2-mercaptobenzothiazole with methoxy group, substrate with nitro group exhibited higher reactivity (entries 3, 7, and 11). In addition, 2-mercaptobenzoxazole was proven to be another type of good candidate for the protocol, showing good



**Scheme 3.**

reactivity which is comparable with 6-methxoy-2-mercaptobenzothiazole (entries 2, 6, and 10). The corresponding products were isolated in high yield (up to 91%) and the definite structure of **3b** was unanimously confirmed by X-ray single crystal diffraction (Fig. 1).[16]

Cyclohexyl isocyanide and 2,6-di-methylphenyl isocyanide were further employed to study the generality of isocyanide. It was obvious to find that 2,6-di-methylphenyl isocyanide showed higher reactivity than cyclohexyl and *tert*-butyl isocyanides (entries 10–12), but the isolated yields of final products were similar to the formers. 2-Mercaptobenzimidazole, which has the similar skeleton with 2-mercaptobenzothiazole and 2-mercaptobenzoxazole, was also selected to test the scope of thio-compound. It can be seen 2-mercaptobenzimidazole was less reactive than other thio-compounds, only poor yields of final products could be obtained. Moreover, in the case of 2,6-di-methylphenyl isocyanide, the reaction could hardly occur and thus no desired product was isolated. We also unexpectedly found that 4,5-dihydrothiazole-2-thiol was almost inert in this reaction. It was supposed that the benzene ring may stabilize the in situ formed intermediate during the reaction process. With this question in mind, we turned our attention to the reaction mechanism and the role of ultrasound irradiation played in the reaction. As is known, isomerization of 2-mercaptobenzothiazole often occurred under basic conditions,[17] leading to the formation of N-centered nucleophiles. Whereas, in our cases, N-centered attachment can take place even without the use of extra base. According to Chupp's findings,[11] an introduction of extra energy, such as heating, can be an alternative method to promote the isomerization of 2-mercaptobenzothiazole. Therefore, we propose the mechanism as follows (Scheme 3): under ultrasonic irradiation condition at 50 °C, 2-mercaptobenzothiazole was isomerized to N-centered nucleophiles with hydrogen transfer to another 2-mercaptobenzothiazole molecule, an ion pair species (**A**) was thus formed. The nitrogen with negative charge then attacked the isocyanide, the latter further attacked the hydrogen attached to the nitrogen atom in **A**. The free 2-mercaptobenzothiazole molecule again went into next cycle. On the basis of above analysis, we believed that the ultrasonic irradiation played an important role in the formation of N-centered nucleophile while this may be the rate-determining step in the reaction. Moreover, the use of ultrasonic irradiation enabled the reaction to proceed smoothly under mild conditions even without the use of inert atmosphere.

In summary, we disclosed an easy access to the formamidine framework by direct reactions of isocyanides with compounds containing active N–H bonds. Ultrasound irradiation was demonstrated to promote the reactions effectively. Moreover, ultrasound irradiation allowed the organic transformations to be performed under mild and catalyst-free conditions without the need of inert atmosphere.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.100.

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15. *General experimental procedure.* To a mixture of 2-mercaptobenzothiazole (0.5 mmol) and *tert*-butyl isocyanide (0.5 mmol) was added 0.1 mL of acetonitrile. The reaction mixture was irradiated by ultrasound in an appropriate time at 50 °C until the thio-compound was completely consumed (checked by TLC). Then the solvent was evaporated under the reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford pure product **3a**.
*3-((Tert-butylimino)methyl)benzo[d]thiazole-2(3H)-thione* (**3a**): white solid; mp: 105–106 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.23 (s, 1H –N=CH–$NR_2$), 8.88 (d, $J$ = 8.5 Hz, 1H-ArH), 7.46–7.37 (m, 2H-ArH), 7.34 (d, $J$ = 7.6 Hz, 1H-ArH), 1.40 (s, 9H –$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.21, 144.47, 140.21, 127.33, 126.48, 125.63, 120.69, 116.97, 57.76, 30.26. HR-MS ($m/z$) calcd for $C_{12}H_{14}N_2S_2$ ($M^+$): 250.0598, found: 250.0606.
16. Crystallographic data for the structure of **3b** reported in this Letter has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 787050. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: +44 01223 336033).
*Structural parameters for* **3b**: data collection: Rigaku Mercury CCD area detector; crystal size: 0.40 × 0.20 × 0.15 $mm^3$; $C_{12}H_{14}N_2OS$, Mr = 234.31, monoclinic, space group P 21/m, $a$ = 9.5881(17), $b$ = 6.7134(10), $c$ = 9.7209(17) Å, β = 101.528(4), $V$ = 613.10(18) $Å^3$, $Z$ = 2, $D_{calcd}$ = 1.269 g $cm^{-3}$, $R[I > 2\sigma(I)]$ = 0.0490, $wR[I > 2\sigma(I)]$ = 0.1134.
17. (a) Halasa, A. F.; Smith, G. E. P., Jr. *J. Org. Chem.* **1973**, *38*, 1353; (b) DAmico, J. J.; Suba, L.; Ruminski, P. G. *J. Heterocyclic Chem.* **1985**, *22*, 1479. and references therein.