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Domino [3+2+1] heterocyclization of isothiocyanates with aryl amidines leading to polysubstituted 1,3,5-triazine derivatives

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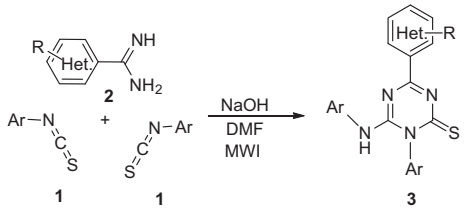
ABSTRACT

Concise and efficient domino [3+2+1] heterocyclization of isothiocyanates with aryl amidines has been established for the synthesis of 1,3,5-triazine derivatives. The multicomponent domino reaction (MDR, AB_2 type) is easy to perform simply by mixing inexpensive isothiocyanates and aryl amidines in the presence of NaOH under microwave heating. The present synthesis shows attractive properties such as concise one-pot conditions, short reaction periods (15–24 min), and easy purifications. The resulting 1,3,5-triazine derivatives are important structural motifs in organic and medicinal research.

Nitrogen-containing heterocycles (azaheterocycles) are omnipresent in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, antibiotics, and alkaloids, as well as pharmaceuticals and many more compounds.[1] The 1,3,5-triazines and their derivatives are the oldest class of extremely important heterocyclic compounds and are used in a wide array of synthetic and industrial applications. They have been found to exhibit anti-tumor,[2] corticotrophin-releasing factor-1 receptor antagonist,[3] leukotriene C4 (LTC4) antagonist,[4] inosine monophosphate dehydrogenase (IMPDH) inhibitory,[5] and erm methyltransferase inhibitory activities.[6] In the past several decades, many methodologies for the preparation of 1,3,5-triazines with different substituents have been developed, which involved nucleophilic substitution of cyanuric chloride with different nucleophiles,[5,7] two-component reaction of biguanides with acid chlorides,[8] or anhydrides,[9] or carboxylates,[6,10] cascade cyclization of acylamidines with amidines or guanidines,[11] two-step method of isothiocyanates,[12] and recently one-pot reaction of isothiocyanates, *N*,*N*-diethylamidines, and carbamidines.[13] However, most of these reactions suffered from multisteps, the limited scope of substrates, tedious operation procedures, and longer reaction times. Therefore, the development of new alternate and more efficient strategies for the synthesis of this family of heterocyclic compounds by minimizing the formation of waste and by-products, continues to be of great interest and challenging.

On the other hand, multicomponent domino reactions (MDRs) allow the creation of several bonds in a single operation and embody many features including atom- and step economy, convergence, structural diversity, and reduction in the number of workup procedures and purification processes, thereby minimizing the generation of waste and rendering the transformations green.[14] Based on the unique properties of intermediates, these processes can be rationally designed, so that they serve as ideal approaches for the efficient synthesis of structurally complex and functionally diverse molecules that play the role of lead compounds in drug discovery efforts.[15] Therefore, MDRs have attracted enormous attention and became a powerful tool in organic chemistry.

Recently, we have been engaging in the development of unique MDRs that can provide easy access to new core structures of chemical and pharmaceutical interest.[16,17] As a part of our study of this topic, we now developed domino [3+2+1] heterocyclization of isothiocyanates with aryl amidines, providing polyfunctionalized 1,3,5-triazine derivatives with good yields (Scheme 1).



Scheme 1. The multicomponent domino reaction of **1** with **2**.

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The great features of this chemistry are shown by the fact that the domino construction of 1,3,5-triazine skeleton and its N-arylation was readily achieved via base-promoted multicomponent reaction (AB_2 type) in a one-pot operation. The present work represents the special example for the preparation of such important types of 1,3,5-triazine derivatives.

In an initial study, benzamidine (**2a**, 1.0 equiv) was reacted with 4-chlorophenyl isothiocyanate (**1a**, 2.2 equiv) in DMF at 80 °C using NaOH (0.2 equiv) as a base under microwave heating. The reaction proceeded smoothly to provide polysubstituted 1,3,5-triazines **3a** in 58% yield. The structure of **3a** was characterized on the basis of its spectral and analytical data. Furthermore, the structural elucidation was unequivocally determined by X-ray diffraction of single crystals of **3j** (Fig. 1) and **3l** (See SI).

Encouraged by the above reported satisfactory results, we next optimized this reaction conditions including different solvents and bases (Table 1). The same reaction of **1a** with **2a** was investigated using a variety of bases (0.2 equiv), such as K_2CO_3, NaOH, Et_3N, and NaOEt under microwave (MW) irradiation at 80 °C. The reaction scarcely proceeded in the presence of K_2CO_3 (Table 1, entry 1). When Et_3N or NaOEt was used as a base catalyst, **3a** was isolated in low yield and this may be due to the formation of thiourea **4** as by-product. (Table 1, entries 2 and 3). Subsequently, the effect of NaOH as a base promoter was investigated in this reaction. 0.2 equiv of NaOH gave 58% yield of the product **3a**. A similar outcome (56%) was observed when the amount of NaOH was increased to 0.4 equiv (Table 1, entry 6). When 0.1 equiv of NaOH was used, it resulted in slightly lower yield of the desired product **3a** (Table 1, entry 5). Next, the reaction promoted by NaOH was performed in different solvents such as EtOH (47%), DMF (58%), and 1,4-dioxane (50%) in a sealed vessel under microwave irradiation for 15 min. The best yield of product **3a** (78%) was obtained in DMF, as the reaction temperature was increased to 110 °C (Table 1, entry 7).

Using the optimized reaction conditions, the scope of a variety of structurally diverse isothiocyanates and aryl amidines were investigated, and a series of new 1,3,5-triazine-2(1*H*)-thiones were synthesized in good yields, with arylamino group in position 6 of the 1,3,5-triazine-2(1*H*)-thione nucleus. As shown in Table 2, we found that the substituents on the aromatic ring of aryl amidines

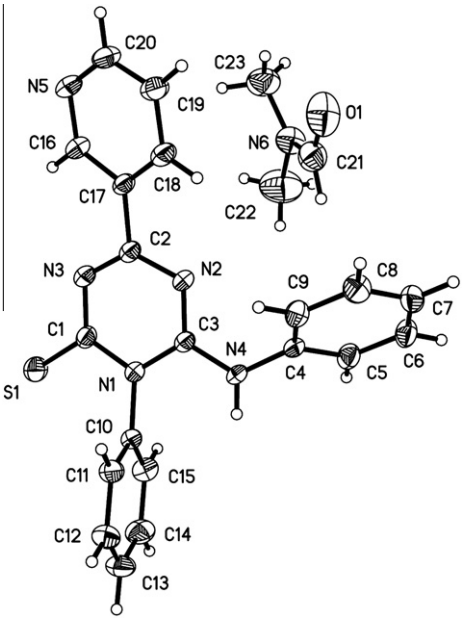
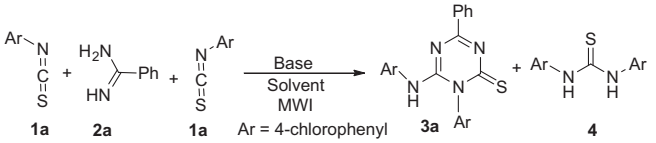


Figure 1. X-ray structure of **3j**.[19]

Table 1
Optimization of reaction conditions



Entry	Base (equiv)	Solvent	*T* (°C)	Time (min)	Yield[a] (%)
1	K_2CO_3 (0.2)	DMF	80	20	Trace
2	Et_3N (0.2)	DMF	80	15	28
3	NaOEt (0.2)	DMF	80	15	35
4	NaOH(0.2)	DMF	80	15	58
5	NaOH (0.1)	DMF	80	15	42
6	NaOH (0.4)	DMF	80	15	56
7	NaOH(0.2)	DMF	110	15	78

[a] Isolated yield.

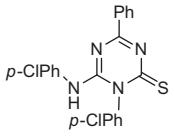
2 did not hamper the reaction progress. Reactions of methyl-, bromo-, chloro-, or fluoro-substituted phenyl isothiocyanates **1** with aryl amidines **2**, all proceeded well to afford the desired products in good yields. Aryl amidines bearing electron-withdrawing groups were examined and as anticipated, the reactions proceeded smoothly to give the corresponding products in good yields. Pyridin-3-yl, pyridin-4-yl, and pyrimidin-2-yl amidines were also converted into pyridin-3-yl, pyridin-4-yl, and pyrimidin-2-yl substituted 1,3,5-triazine-2(1*H*)-thiones **3c–3e**, **3h–3i**, **3l–3n**, **3q–3s**, and **3u–3v** and the products were isolated in 60–78% yields. The results exhibited the scope and generality of the new domino reaction with respect to a range of amidine and isothiocyanate substrates. Furthermore, halogen (Cl, and Br) containing substrates were also well tolerated. These functional groups provide ample opportunity for further functional group manipulations such as using modern cross-coupling reactions.

Similar to our previous domino processes,[16,17] the present reaction also showed the following attractive characteristics: (1) fast reaction rates which enable the reaction to be completed within 15–24 min; (2) the convenient work-up which only needs simple filtration since, the products directly precipitate out after the reaction is finished and when its mixtures were neutralized with dilute hydrochloric acid; (3) purification by chromatography can be avoided, and the pure products can be easily acquired only by washing the crude products with 95% EtOH; (4) simple and available substrates of amidines and isothiocyanates. Moreover, during these domino processes, the construction of 1,3,5-triazine-2(1*H*)-thione ring was accompanied by C=S and C=N bonds cleavage of the isothiocyanates.

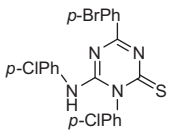
A plausible mechanism was proposed in Scheme 2. We hypothesized that amidines **2** would attack isothiocyanates **1** first in the presence of a base to generate an intermediate **A**, and then a second addition between **A** and the second molecule of isothiocyanates **1** occurred, leading to bis-thiourea intermediate **B**, which underwent intramolecular cyclization and subsequent dethiolation to furnish the compound **3**.

In summary, we have described a base-promoted domino [3+2+1] heterocyclization as an alternative method for the synthesis of a series of *N*-arylamino substituted 1,3,5-triazines with concomitant formation of three sigma-bonds in a one-pot manner. This reaction provides a facile and efficient strategy for the construction of structurally diverse 1,3,5-triazine skeleton. Features of this strategy include short reaction times (15–24 min) and convenient one-pot operation. Further investigations are in progress in

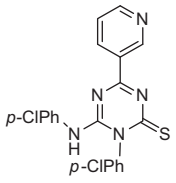
Table 2
Syntheses of products **3**[18]



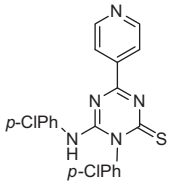
3a, 15 min, 78%



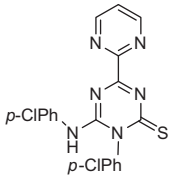
3b, 18 min, 70%



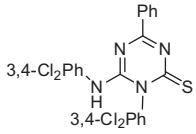
3c, 22 min, 76%



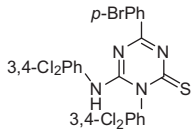
3d, 20 min, 72%



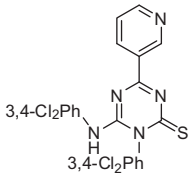
3e, 24 min, 63%



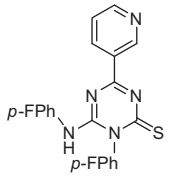
3f, 15 min, 78%



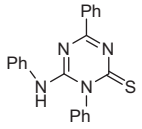
3g, 18 min, 72%



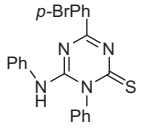
3h, 15 min, 75%



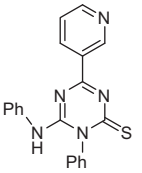
3i, 22 min, 70%



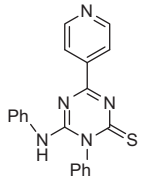
3j, 15 min, 84%



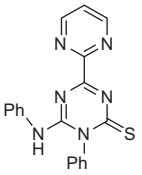
3k, 18 min, 70%



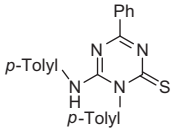
3l, 16 min, 78%



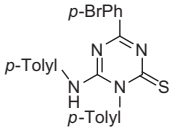
3m, 15 min, 75%



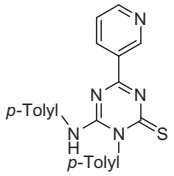
3n, 20 min, 60%



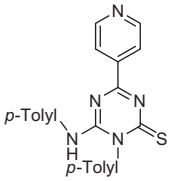
3o, 15 min, 79%



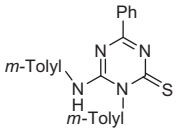
3p, 18 min, 72%



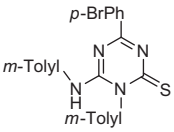
3q, 18 min, 78%



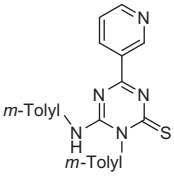
3r, 16 min, 75%



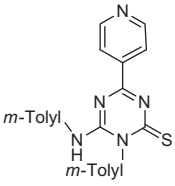
3s, 22 min, 76%



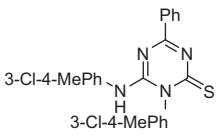
3t, 24 min, 75%



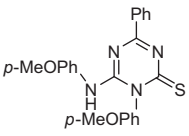
3u, 18 min, 76%



3v, 20 min, 74%



3w, 20 min, 77%



3x, 24 min, 84%

our laboratory to synthesize more complex products containing 1,3,5-triazine core and test their biological activity.

Acknowledgments

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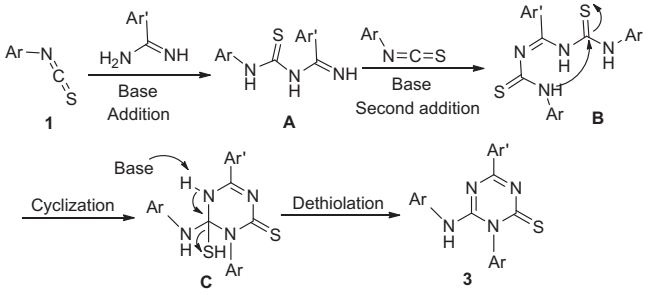

Scheme 2. The plausible mechanism for the formation of 1,3,5-triazines **3**.

Supplementary data

Supplementary data (experimental details and spectroscopic characterization of all compounds along with 1H, IR and mass spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.086.

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18. *General procedure for the synthesis of compounds* **3**: In a 10 mL reaction vial, benzamidine **2a** (1.0 mmol), sodium hydroxide (0.2 mmol) and DMF (2.0 mL) were mixed and then stirred for 10 min. Subsequently, the 4-chlorophenyl isothiocyanate **1a** (2.2 mmol) was added to the reaction mixture, and the reaction vial was capped and pre-stirring for 20 s. The mixture was subjected to microwave irradiation (time: 15 min, temperature: 110 °C; absorption level: high; fixed hold time). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and was neutralized with 10% hydrochloric acid. Then, the system was poured into the cool water and was filtered to give crude product. The crude product was further purified by 95% EtOH to give the corresponding pure products **3**. *6-(4-chlorophenylamino)-1-(4-chlorophenyl)-4-phenyl-1,3,5-triazine-2(1H)-thione (**3a**)*, Yellow solid, Mp 262–263 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.08 (s, 1H, NH), 8.20 (d, J = 6.8 Hz, 2H, ArH), 7.67 (d, J = 7.6 Hz, 2H, ArH), 7.68–7.42 (m, 9H, ArH), ^{13}C NMR (100 MHz, DMSO-d_6) δ: 185.8, 163.1, 156.2, 137.3, 136.4, 134.0, 131.8, 131.1, 130.7, 130.3, 130.1, 129.4, 127.3, 127.0, 125.9. IR (KBr, ν, cm^{-1}): 3373, 1593, 1553, 1471, 1429, 1348, 1224, 1091, 1004, 988, 759, 705. HRMS (ESI): m/z calcd for $C_{21}H_{13}Cl_2N_4S$, 423.0232 $[M-H]^-$; found: 423.0241.
19. The single-crystal growth was carried out in DMF at room temperature. Crystal data for **3l** (CCDC-916140): $C_{43}H_{37}N_{11}OS_2$, crystal dimension 0.40 × 0.30 × 0.21 mm, Monoclinic, space group C2/c, a = 21.438(2) Å, b = 11.0408(12) Å, c = 19.503(2) Å, $\alpha = \gamma = 90°$, β = 121.573(2)°, V = 3933.0(8) Å^3, Mr = 787.96, Z = 4, λ = 0.71073 Å, μ(Mo Kα) = 0.186 mm^{-1}, F(000) = 1648, R_1 = 0.0423, wR_2 = 0.0925.