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Efficient Synthesis of Polyfunctionalized Pyrimidine Derivatives

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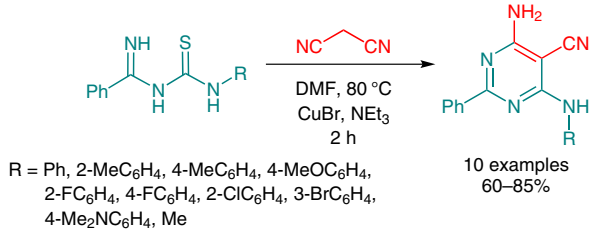

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Abstract A simple and direct procedure was developed for the synthesis of a novel series of polyfunctionalized pyrimidines. They were prepared via reaction of *N*-(substituted carbamothioyl)benzimidamides (prepared from the reaction of benzimidamide hydrochloride and isothiocyanates) and malononitrile in the presence of $CuBr/Et_3N$ in DMF at 80 °C.

Key words pyrimidines, heterocycles, isothiocyanates, malononitrile

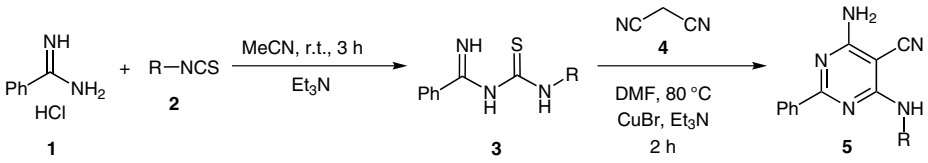
Pyrimidine and its derivatives[1] are of great importance in nature since they are ubiquitous in many natural products such as vitamin B_1.[2] Also, they are present in a broad spectrum of synthetic biologically active derivatives such as uramustine, floxuridine, and fluorouracil (antineoplastic agents), piromidic acid, tetroxoprim, and metioprim (antibacterial agents), flucytosine (antifungal agent), idoxuridine and broxuridine (antiviral agents), piribedil (antiparkinsonian agent), and tisopurine (antihyperuricaemia agent).[3] Pyrimidines are considered as an integral part of the nucleic acid structure which plays an important role in various biological processes.[4] Also, metal complexes of pyrimidine moiety have shown antimicrobial and antibacterial activities.[5] Therefore, pyrimidines would be a major candidate for the challenge of modern drug-discovery research, and efficient methods for the synthesis of versatile derivatives are still in demand.

Pyrimidines are usually synthesized through cyclization reaction of β-dicarbonyl derivatives with N–C–N compounds including amidines, ureas, and guanidines.[6] In this regard, i) reaction of aromatic aldehydes, ketones, and guanidine carbonate,[7] as well as ii) Biginelli-type multicomponent reactions[8] have been largely considered in the literature. Recently, novel methods for the synthesis of pyrimidines have been established. In this regard, microwave-assisted condensation of cyanic acid derivatives with *N*-vinyl/aryl amides in the presence of $SmCl_3$,[9] the coupling of acid chlorides with terminal alkynes in the presence of Et_3N followed by the reaction of amines or amidinium salts,[10] and reaction of *N*-vinyl tertiary enamide and isocyanides using Tf_2O[11] have been successfully developed.

In recent years, using isothiocyanates as a versatile starting material has been developed for the synthesis of various heterocyclic compounds.[12–14] At this juncture, synthesis of nonsulfur heterocycles needs efficient desulfurizing agents such as $HgCl_2$,[15,16] molecular iodine,[17–23] DCC,[24] CuCl,[25] and CuI[26] were found to be effective in various organic transformations including a desulfurization step. In this work, focusing on the efficiency of isothiocyanates and in continuation of our research program on the synthesis of novel heterocycles,[27] we describe an efficient procedure for the preparation of novel polyfunctionalized pyrimidines **5** through the reaction of *N*-(substituted carbamothioyl)benzimidamides **3** and malononitrile (**4**) in the presence of $CuBr/Et_3N$ in DMF at 80 °C (Scheme 1).

For the preparation of desirable pyrimidine derivatives **5**, the required starting materials, *N*-(substituted carbamothioyl)benzimidamides **3** were prepared from the reaction of benzimidamide hydrochloride (**1**) and isothiocyanates **2** (Scheme 1). For this purpose, reaction of equivalent amounts of benzimidamide hydrochloride (**1**) and isothiocyanates **2** in the presence of a twofold amount of Et_3N in acetonitrile at room temperature gave the corresponding compounds in good yield (75%).[28] Next, reaction of compound **3** and malononitrile (**4**) was investigated under various conditions.

Firstly, *N*-(phenylcarbamothioyl)benzimidamide (**3a**) was selected as a model substrate, and its reaction with malononitrile (**4**) was screened in a range of solvents and desulfurizing agents at different temperature levels (Table



Scheme 1 Synthesis of novel pyrimidine derivatives **5**

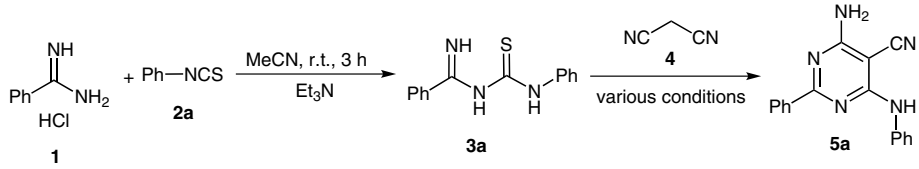
1). As reported in Table 1, the model reaction was conducted in the presence of different copper salts such as CuBr, $CuBr_2$, CuI, as well as $HgCl_2$, EDCI, and $AgNO_3$. Our results revealed that $HgCl_2$ and CuBr were more effective than the other reagents and promoted the cyclization reaction efficiently. Clearly, CuBr was the best choice due to the mercury toxicity, in spite the fact that $HgCl_2$ gave better yield (Table 1, entries 1 and 2).

To obtain the best yield, the model reaction was investigated in the presence of various amounts of CuBr. It was found that an equivalent amount of CuBr was sufficient and higher amounts did not lead to better conditions. The important thing is related to the necessity of using base in the reaction.

It was revealed that a fourfold amount of Et_3N was necessary to give the corresponding product **5a** in good yield, and using lower amounts of base led to the lower yield of product. Also, various organic solvents such as DMF, dichloromethane, toluene, and THF were examined, and DMF was found to be the more effective medium. Temperature screening revealed that the model reaction proceeded slowly at room temperature and when it was heated at 80 °C, the corresponding product **5a** was obtained in 85% yield.

With these results in hand, various *N*-(substituted carbamothioyl)benzimidamides **3a–j** were reacted with malononitrile (**4**) under the optimized conditions to obtain different polyfunctionalized pyrimidines **5** (Table 2). All substrates possessing electron-rich as well as electron-poor substituents underwent the cyclization reaction leading to the formation of the related products **5** within two hours in good yields. All products were characterized using IR and NMR spectroscopy as well as elemental analysis.

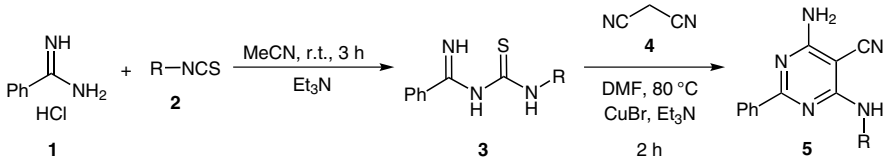
Table 1 Effect of Various Conditions on the Reaction of *N*-(Phenylcarbamothioyl)benzimidamide (**3a**) and Malononitrile (**4**) for Obtaining Product **5a**



Entry	Solvent	Reagent[a]	Temp	Time (h)	Yield (%)[b]
1	DMF	$HgCl_2$	80 °C	2	95
2	DMF	CuBr	80 °C	2	85
3	DMF	CuI	80 °C	2	60
4	DMF	$CuBr_2$	80 °C	2	n.r.[c]
5	DMF	EDCI	80 °C	2	50
6	DMF	$AgNO_3$	80 °C	2	n.r.[c]
7	DMF	CuBr	r.t.	3	10
8	DMF	CuBr	40 °C	3	40
9	DMF	CuBr	80 °C	3	85
10	DMF	CuBr	100 °C	2	85
11	THF	CuBr	reflux	3	50
12	toluene	CuBr	reflux	3	40
13	CH_2Cl_2	CuBr	reflux	3	25

[a] All reactions were performed in the presence of an equivalent amount of desulfurizing agent.
[b] Isolated yields.
[c] No reaction.

Table 2 Synthesis of Polyfunctionalized Pyrimidines **5**



Entry	R	Product **5**	Yield (%)[a]
1	Ph	**5a**	85
2	2-MeC_6H_4	**5b**	72
3	4-MeC_6H_4	**5c**	74
4	4-MeOC_6H_4	**5d**	76
5	2-FC_6H_4	**5e**	63
6	4-FC_6H_4	**5f**	64
7	2-ClC_6H_4	**5g**	67
8	3-BrC_6H_4	**5h**	70
9	4-$Me_2NC_6H_4$	**5i**	78
10	Me	**5j**	60

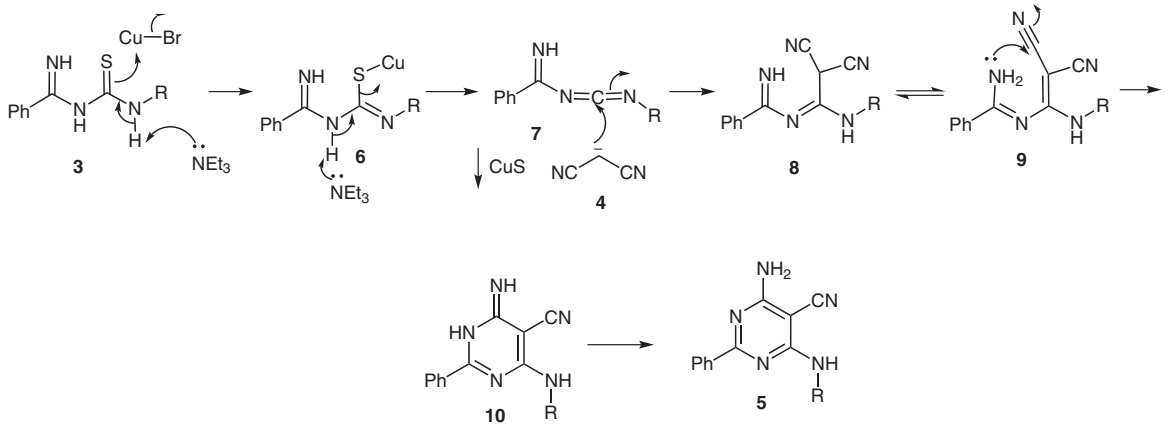
[a] Isolated yields.

The proposed mechanism is shown in Scheme 2. Loss of CuS from the activated intermediate **6** gives carbodiimide intermediate **7**. It is attacked by malononitrile (**4**) in the presence of Et_3N to obtain **8** which is in equilibrium with intermediate **9**. Next, intramolecular cyclization of the intermediate **9** following tautomerization of the intermediate **10** leads to the formation of title compounds **5**.

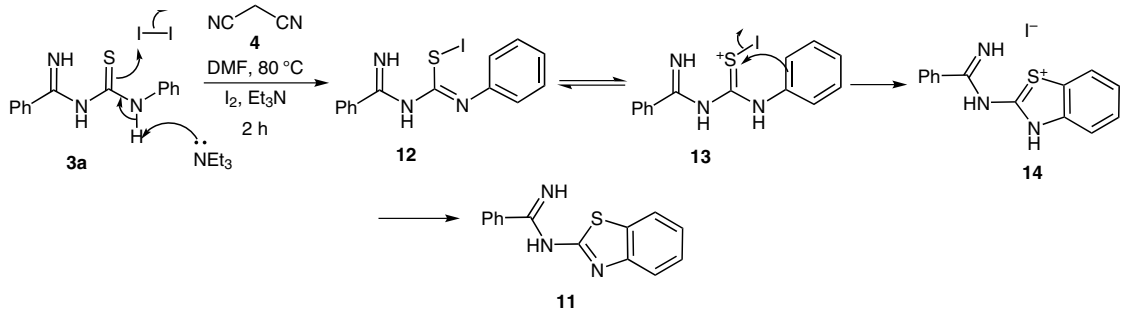
During our investigations, focusing on the efficiency of molecular iodine as a desulfurizing agent, the model reaction was achieved in the presence of I_2 (Scheme 3). Interestingly, the desired product **5a** was not obtained. Our results revealed that a different synthetic route as reported in the literature[17] proceeded and *N*-{benzo[*d*]thiazol-2-yl}benzimidamide (**11**) was the main product.

Analysis of spectroscopic data revealed that malononitrile (**4**) did not participate in the reaction. It seems that the deprotonation of **3a** gave intermediate **12**, in equilibrium with intermediate **13**, which underwent an intramolecular substitution to form thiazole ring **14** followed by proton transfer to afford compound **11** (Scheme 3).

In conclusion, we have developed an efficient strategy for the preparation of a novel series of polyfunctionalized pyrimidines through the reaction of *N*-(substituted carbamothioyl)benzimidamides (prepared from the reaction of benzimidamide hydrochloride and isothiocyanates) and malononitrile in the presence of CuBr/Et_3N in DMF at 80 °C. A practical and easy approach for the preparation of novel polyfunctionalized pyrimidines makes this work beneficial



Scheme 2 Proposed mechanism for the formation of product **5**



Scheme 3 Investigation of the model reaction in the presence of I_2

for both organic and medicinal chemists to develop novel pyrimidine-based drugs. Also, it was found that if the reaction was conducted in the presence of molecular iodine, a different synthetic route proceeded and *N*-benzo[*d*]thiazole was obtained.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561381.

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