

# Novel Synthesis of 1-Aroyl-3-aryl-4-substituted Imidazole-2-thiones

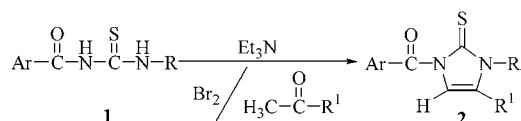
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## ABSTRACT



**2a-f** Ar = Ph, R<sup>1</sup> = CH<sub>3</sub>    **4a-f** Ar = *o*-ClC<sub>6</sub>H<sub>4</sub>, R<sup>1</sup> = CH<sub>3</sub>

**5a-f** Ar = Ph, R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>    **6a-f** Ar = Ph, R<sup>1</sup> = H

An efficient route to 1-aryloyl-3-aryl-4-substituted imidazole-2-thiones (**2**, **4–6**) has been developed. The methodology involves the cyclization of 1-aryloyl-3-arylthioureas with a variety of carbonyl compounds bearing  $\alpha$ -H in the presence of bromine and triethylamine.

Imidazole-2-thione and its derivatives have received attention because of their bioactivities and application for pharmaceutical synthesis.<sup>1,2</sup> Marckwald established the first synthetic route to 1-substituted imidazole-2-thione by reaction of isothiocyanate with aminoacetal in 1889.<sup>3</sup> Lawson prepared imidazole-2-thione and its derivatives from KNCS and the corresponding amino acid ester hydrochloride.<sup>4</sup> Matsuda modified Marckwald's method into a one-pot fashion in 1997.<sup>1</sup> In recent years, imidazole-2-thione nucleosides have received much attention. Palacios reported the synthesis of optically pure 1-aryl-5-hydroxy-4-(D-arabino-tetritol-1-yl)-imidazolidine-2-thione, which may be used as chiral auxil-

iaries and ligands for asymmetric catalysis.<sup>5</sup> Fuentes described the reaction of D-fructosamines with different sugar isothiocyanates to obtain chiral imidazolidine-2-thione N-nucleosides.<sup>6</sup> Furthermore, the same author used imidazolidine-2-thione C-nucleoside as a precursor for the synthesis of azidonucleosides and fluoronucleosides; these compounds are of pharmaceutical interest due to their anti-AIDS activity.<sup>7</sup> A few years ago, we developed a new method for the preparation of 1,5-disubstituted-2,4-imidazolidinedione and 1,5-disubstituted 2-thioxo-4-imidazolidinones by the reaction of  $\alpha$ -keto hemithioacetal with ureas and thioureas.<sup>8</sup> In this communication, we wish to describe a novel synthesis of 1-aryloyl-3-aryl-4-substituted imidazole-2-thiones (**2**, **4–6**).

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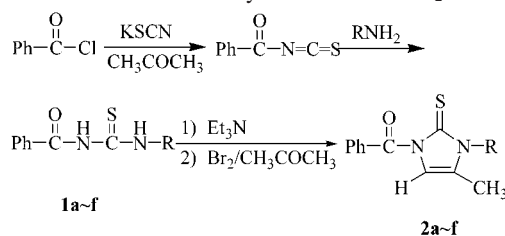
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In the course of our search for compounds bearing bioactivities, we required some thiazole derivatives such as 2-benzoylamino benzothiazole. Therefore, the reaction of 1-benzoyl-3-phenylthiourea (**1a**) and  $K_3Fe(CN)_3$  in basic medium was explored, but the expected products were not formed. Furthermore, the reactions of **1a** and bromine in chloroform or other organic solvents were also explored, but the expected products were not found. However, when the same reaction was performed in acetone, one main spot was detected by TLC, and after normal isolation, a small amount of a pure compound was obtained, whose structure was confirmed to be 1-benzoyl-3-phenyl-4-methylimidazole-2-thione (**2a**) by  $^1H$  NMR,  $^{13}C$  NMR, DEPT, IR, HRMS, and elemental analysis.

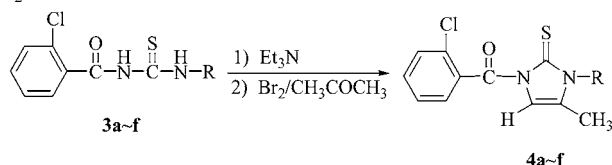
**Table 1.** Reaction of 1-Benzoylthioureas with  $Br_2$ /Acetone



1, 2	product 2		
	R	yield (%)	mp (°C)
<b>a</b>	Ph	75	157~159
<b>b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	82	209~211
<b>c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	84	192~194
<b>d</b>	4-IC <sub>6</sub> H <sub>4</sub>	70	205~207
<b>e</b>	2-Cl-4-F-C <sub>6</sub> H <sub>3</sub>	70	196~198
<b>f</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	78	215~217

According to the structure of **2a**, it is obvious that the solvent acetone was involved in the reaction in the presence of bromine. We think that base may facilitate the reaction. Therefore, triethylamine was added into the system, and the

**Table 2.** Reaction of 1-(*o*-Chlorobenzoyl)thioureas with  $Br_2$ /Acetone



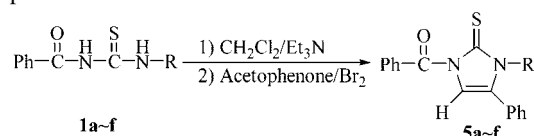
3, 4	product 4		
	R	yield (%)	mp (°C)
<b>a</b>	C <sub>6</sub> H <sub>5</sub>	80	176~177
<b>b</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	87	135~136
<b>c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	89	180~181
<b>d</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	70	170~171
<b>e</b>	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	75	156~157
<b>f</b>	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	82	106~107

reaction was found to be complete in 30 min. Later, this reaction was extended to the other 1-benzoyl-3-arylthioureas, and the corresponding 1-benzoyl-3-aryl-4-methylimidazole-2-thiones (**2b-f**) were obtained (Table 1).

To further demonstrate the scope of the reaction, the cyclization of 1-(*o*-chlorobenzoyl)-3-arylthioureas (**3**) and  $Br_2$ /acetone in the presence of triethylamine were carried out, and similar results were obtained (Table 2).

On the basis of the above results, we tried to use acetophenone instead of acetone. The expected products, 1-benzoyl-3-aryl-4-phenylimidazole-2-thiones (**5**), were obtained (Table 3).

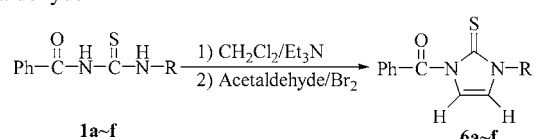
**Table 3.** Reaction of 1-Benzoylthioureas with  $Br_2$ /Acetophenone



1, 5	product 5		
	R	yield (%)	mp (°C)
<b>a</b>	Ph	85	208~210
<b>b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	83	215~217
<b>c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	87	233~235
<b>d</b>	4-IC <sub>6</sub> H <sub>4</sub>	88	249~251
<b>e</b>	2-Cl-4-F-C <sub>6</sub> H <sub>3</sub>	86	242~244
<b>f</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	76	268~270

The success of synthesis of compounds **5** prompted us to further explore the reaction of **1** with acetaldehyde. Similar products, 1-benzoyl-3-aryl-4-phenylimidazole-2-thiones (**6**), were prepared (Table 4).

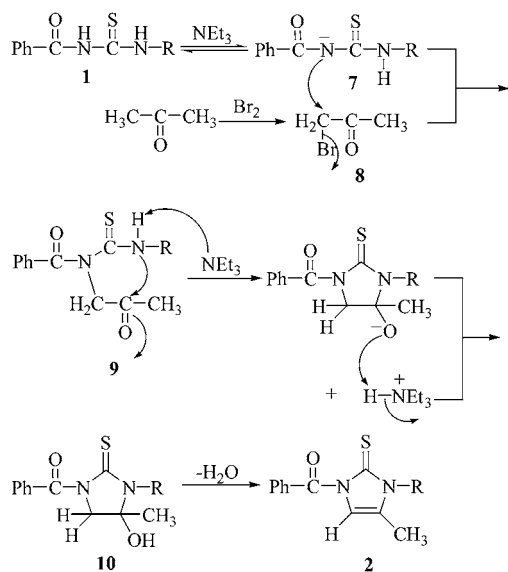
**Table 4.** Reaction of 1-Benzoylthioureas with  $Br_2$ /Acetaldehyde



1, 6	product 6		
	R	yield (%)	mp (°C)
<b>a</b>	Ph	93	105~106
<b>b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	85	205~207
<b>c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	81	221~223
<b>d</b>	4-IC <sub>6</sub> H <sub>4</sub>	92	216~218
<b>e</b>	2-Cl-4-F-C <sub>6</sub> H <sub>3</sub>	93	208~210
<b>f</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	89	166~168

According to the structures of **2**, we can propose a mechanism for the reaction of 1-benzoyl-3-arylthioureas (**1**) with  $Br_2$ /acetone in the presence of triethylamine (Scheme

Scheme 1



1). Triethylamine attacks the 1-H of 1-benzoyl-3-arylthioureas (**1**) in the first step. Bromoacetone (**8**) is produced in situ by bromination of acetone, and the carbon of the bromomethyl group of **8** is attacked by the 1-nitrogen atom

of **7** to form intermediate **9**. The 3-H of **9** is attacked by triethylamine, followed by intramolecular attack of the carbonyl by the 3-nitrogen and hydrogen transfer to give **10** and loss of H<sub>2</sub>O from **10** to afford compounds **2**. The formation of compounds **4–6** can be explained by a similar mechanism.

In conclusion, we have developed a good method for the preparation of 1-aryl-3-aryl-4-substituted imidazole-2-thiones (**2**, **4–6**) from the cyclization of 1-aryl-3-arylthioureas with a variety of carbonyl compounds bearing  $\alpha$ -H such as acetone, acetophenone, and acetaldehyde in the presence of bromine and triethylamine.

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**Supporting Information Available:** General procedure for preparation of **2**; IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, HRMS, and elemental analysis for **2a–f**; HRMS for **4a–f**; IR, <sup>1</sup>HNMR, and HRMS for **5a–f**; <sup>1</sup>HNMR, <sup>13</sup>CNMR, and HRMS for **6a–c,f**; and HRMS for **6d–e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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