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

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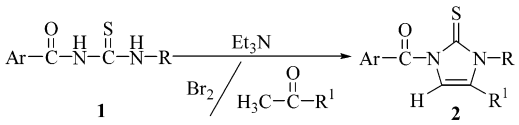
ABSTRACT



An efficient route to 1-aroyl-3-aryl-4-substituted imidazole-2-thiones (2, 4–6) has been developed. The methodology involves the cyclization of 1-aroyl-3-arylthioureas with a variety of carbonyl compounds bearing α-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.[1,2] Marckwald established the first synthetic route to 1-substituted imidazole-2-thione by reaction of isothiocyanate with aminoacetal in 1889.[3] Lawson prepared imidazole-2-thione and its derivatives from KNCS and the corresponding amino acid ester hydrochloride.[4] Matsuda modified Marckwald's method into a one-pot fashion in 1997.[1] 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 auxiliaries and ligands for asymmetric catalysis.[5] Fuentes described the reaction of D-fructosamines with different sugar isothiocyanates to obtain chiral imidazolidine-2-thione N-nucleosides.[6] 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.[7] 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 α-ketohemithioacetal with ureas and thioureas.[8] In this communication, we wish to describe a novel synthesis of 1-aroyl-3-aryl-4-substituted imidazole-2-thiones (**2**, **4**−**6**).

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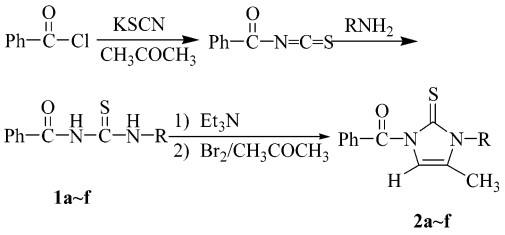
In the course of our search for compounds bearing bioactivities, we required some thiazole derivatives such as 2-benzoylamino benzothiazole. Therefore, the reaction of 1-benzoyl-3-phenylthiourea (**1a**) and $K_3Fe(CN)_3$ in basic medium was explored, but the expected products were not formed. Furthermore, 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

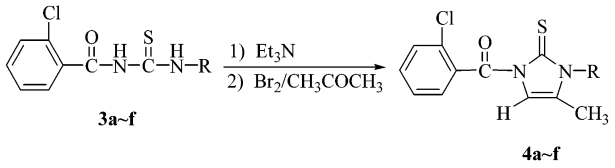


	product **2**		
1, **2**	R	yield (%)	mp (°C)
a	Ph	75	157~159
b	4-ClC_6H_4	82	209~211
c	4-BrC_6H_4	84	192~194
d	4-IC_6H_4	70	205~207
e	2-Cl-4-F-C_6H_3	70	196~198
f	4-$CH_3C_6H_4$	78	215~217

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 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).

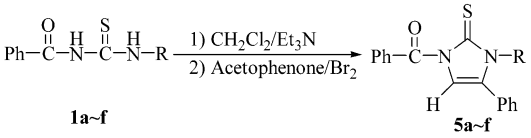
Table 2. Reaction of 1-(*o*-Chlorobenzoyl)thioureas with Br_2/Acetone



	product **4**		
3, **4**	R	yield (%)	mp (°C)
a	C_6H_5	80	176~177
b	$C_6H_5CH_2$	87	135~136
c	4-BrC_6H_4	89	180~181
d	4-$CH_3OC_6H_4$	70	170~171
e	2-$CH_3C_6H_4$	75	156~157
f	3-$CH_3C_6H_4$	82	106~107

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).

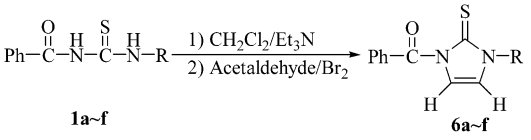
Table 3. Reaction of 1-Benzoylthioureas with Br_2/Acetophenone



	product **5**		
1, **5**	R	yield (%)	mp (°C)
a	Ph	85	208~210
b	4-ClC_6H_4	83	215~217
c	4-BrC_6H_4	87	233~235
d	4-IC_6H_4	88	249~251
e	2-Cl-4-F-C_6H_3	86	242~244
f	4-$CH_3C_6H_4$	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-arylimidazole-2-thiones (**6**), were prepared (Table 4).

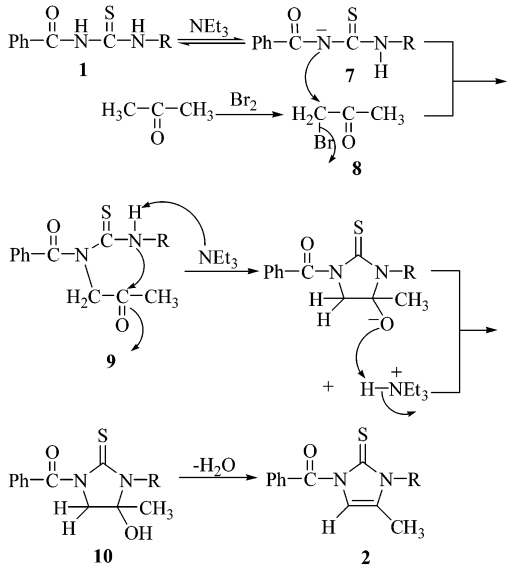
Table 4. Reaction of 1-Benzoylthioureas with Br_2/Acetaldehyde



	product **6**		
1, **6**	R	yield (%)	mp (°C)
a	Ph	93	105~106
b	4-ClC_6H_4	85	205~207
c	4-BrC_6H_4	81	221~223
d	4-IC_6H_4	92	216~218
e	2-Cl-4-F-C_6H_3	93	208~210
f	4-$CH_3C_6H_4$	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_2O 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-aroyl-3-aryl-4-substituted imidazole-2-thiones (**2**, **4**−**6**) from the cyclization of 1-aroyl-3-arylthioureas with a variety of carbonyl compounds bearing α-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, ^{1}HNMR, ^{13}CNMR, HRMS, and elemental analysis for **2a**−**f**; HRMS for **4a**−**f**; IR, ^{1}HNMR, and HRMS for **5a**−**f**; ^{1}HNMR, ^{13}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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