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A Facile Synthesis of New 4-Amino-2-iminothiazoles from Unsymmetrical Thioureas

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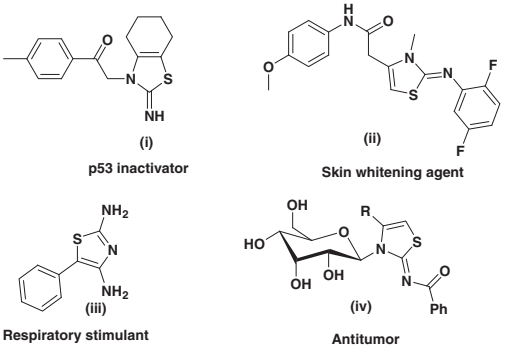
An efficient methodology for the synthesis of 4-amino-2-iminothiazole derivatives has been developed. The synthesis involves the cyclization of unsymmetrical 1-aroyl-3-arylthioureas with a variety of 2-bromo-2-phenylacetonitriles bearing α-H in the presence of triethylamine and acetonitrile.

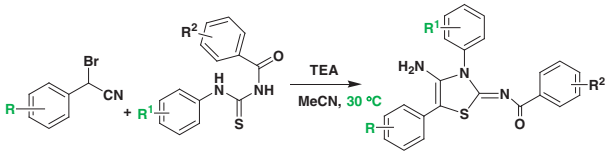
2-Aminothiazole and its isomeric derivatives 2-iminothiazoles are important structural scaffolds that are providing a broad spectrum of biological activities.[1] In particular, 2-iminothiazole derivatives exhibit muscarinomimetic, antimicotic, antidiabetic, anti-inflammatory, antianalgesic, and antibacterial activities.[2] It has been reported that the manipulation of substitution on 2-iminothiazole core unit leads to a different bioactivity. For instance, pifithrin (Pft-α) (i) is a cyclohexane-fused 2-iminothiazole derivative which inactivates p53 human tumor cell lines.[3] While compound (ii) and compound (iv) have the same core unit with different activity, compound (iii) has a different core with different activity, represented in Scheme 1.[4] Hence the synthesis of various functionalized 2-imino or 2-aminothiazoline derivatives is an interesting topic in recent times.[5]

In general, 2-iminothiazoline derivatives were synthesized by the Hantzsch reaction from the corresponding thiourea and α-halocarbonyl compounds. This method leads to a mixture of regioisomers depending upon the reaction conditions.[6] Other than the Hantzsch reaction, several protocols have been documented in literature for the synthesis of 2-iminothiazoline derivatives; i.e., the reaction of α-haloimines with potassium thiocyanate,[7] the reaction of *N*,*N*′-dialkylthiourea with α-halocarbonyl compounds in the presence of base,[8] the reaction of 1,2-diaza-1,3-dienes with thiocyanic acid[9] and other methods.[10] Recently, Zhang and co-workers reported a four component tandem sequence for the synthesis of 2-iminothiazoline derivatives from readily available terminal alkynes, elemental sulfur, carbodiimides, and acid chlorides.[11] Although several procedures have been reported[12] for the synthesis of different substituted 2-iminothiazoline derivatives, none of those procedures utilized the 2-bromo-2-phenylacetonitrile as coupling partner with thiourea derivative. Hence, herein we wish to report the synthesis of 4-amino-2-imino-3-arylthiazoline derivatives by the reaction of benzoylthiourea derivatives with corresponding 2-bromo-2-phenylacetonitrile derivatives in the presence of triethylamine, represented in Scheme 2. In fact, these kinds of compounds were synthesized from the reaction of α-cyanobenzyl benzenesulfonates and thiourea derivatives.[13]

Initially, we synthesized various thiourea derivatives[14] and 2-bromo-2-phenylacetonitriles by using known procedures reported elsewhere. We then attempted the reaction by taking *N*-benzoyl-*N*′-phenylthiourea and 2-bromo-2-phenylacetonitrile as starting materials in the presence of triethylamine. When the reaction was carried out by taking both the reagents in equimolar ratio (1:1) in one lot addition it resulted in the formation of the desired product in poor yield. In order to improve the yield of the desired product, we have screened several reaction conditions. First, we screened various solvents like acetonitrile, chloroform, dichloromethane (DCM), and ethanol for this reaction; we found the reaction more efficient in acetonitrile than the other solvents tested as described in Table 1. As it was known from the literature that triethylamine works as the best base for this kind of transformation,[8d] we also used the same base in our method. To estimate the ratio of the reagents, we carried out the reaction by taking different proportions of reagents. We obtained the best results when benzoylthiourea, 2-bromo-2-phenylacetonitrile, and triethylamine were taken in the ratio of 1:1.1:1.5 equivalents respectively and the reaction should be performed at room temperature, dropwise addition of 2-bromo-2-phenylacetonitrile to the mixture of thiourea derivative and triethylamine.



Scheme 1. Compounds comprising 2-imino or 2-aminothiazoline moiety having different activities.



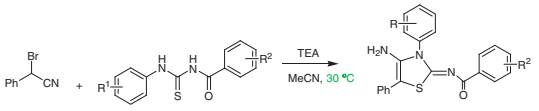
Scheme 2. Our synthetic approach.

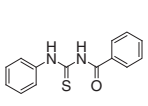
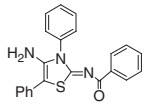
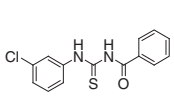
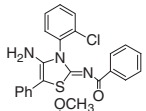
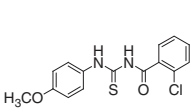
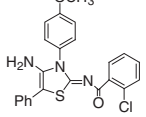
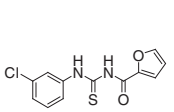
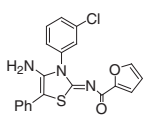
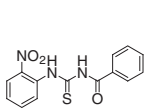
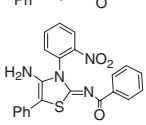
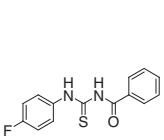
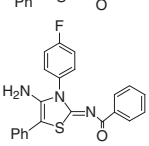
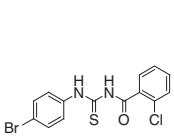
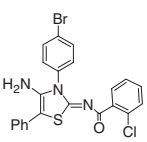
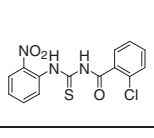
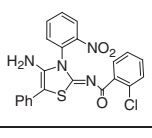
Table 1. Thiazole derivatives under different solvent systems

Entry	Solvent	Time	Yield/%[a]
1	CH_3CN	30 min	96
2	$CHCl_3$	3 h	40
3	DCM	3.5 h	50
4	EtOH	4 h	45

[a]Isolated yields.

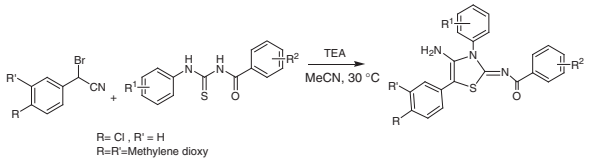
Table 2. Reactions of various aroylthiourea derivatives with 2-bromo-2-phenylacetonitrile in the presence of Et_3N

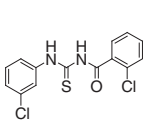
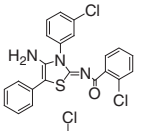
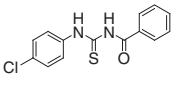
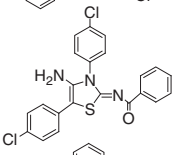
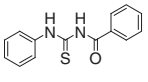
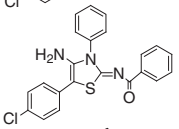
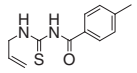
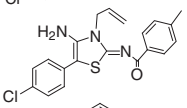
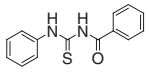
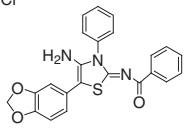
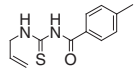
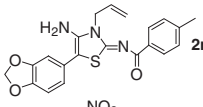
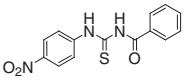
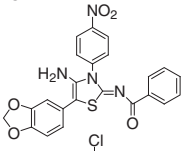
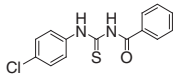
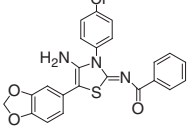


Entry	Substrate	Product	Time/min	Yield/%[a,b]
1		 **2a**[16]	20	80
2		 **2b**	30	82
3		 **2c**	27	89
4		 **2d**	30	80
5		 **2e**	30	86
6		 **2f**	26	90
7		 **2g**	25	88
8		 **2h**	25	87

[a]Reactions performed in 10 mmol scale. Details of reaction conditions are shown in ref. 15. [b]Isolated yields.

Table 3. Reactions of various aroylthiourea derivatives with different 2-bromo-2-phenylacetonitriles in the presence of Et_3N



Entry	Substrate	Product	Time/min	Yield/%[a,b]
1		 **2i**	20	80
2		 **2j**	20	80
3		 **2k**	20	80
4		 **2l**	40	78
5		 **2m**	35	86
6		 **2n**	30	88
7		 **2o**	20	85
8		 **2p**	40	76

[a]Reactions performed in 10 mmol scale. Details of reaction conditions are shown in ref. 15. [b]Isolated yields.

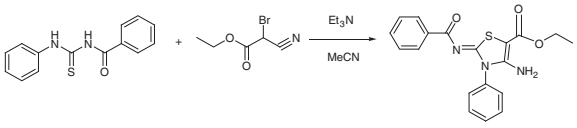
Under these conditions, we obtained the desired product in 80% yield along with a trace of unidentified product which was washed out with hexane. The product was fully characterized by using spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, and MS). In the IR spectrum, the characteristic peak for NH_2 was observed at 3340–3222 cm^{-1} and C=N was observed at 1590–1550 cm^{-1}. In ^{1}H NMR, NH_2 appeared as a broad singlet at 3.5 ppm.

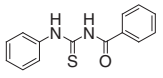
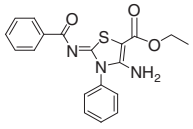
After optimizing the reactions, we focused our attention on exploring the scope and generality of the method with respect to various aroylthiourea derivatives and 2-bromo-2-phenylacetonitrile. The results are summarized in Table 2. As can be seen from Table 2, the reactions of various aroylthiourea derivatives occurred smoothly to produce their corresponding of 4-amino-2-iminothiazoline derivatives in good to excellent yields.

It should be noted that the substitution on the aroylthiourea derivatives has considerable effect on reaction. Under the present reaction conditions sensitive aryl ring such as furfuryl ring survived and gave good yield of its corresponding product.

Encouraged by the successful application of the reaction conditions to various thiourea derivatives with 2-bromo-2-phenylacetonitrile, we further focused our attention to make use of other substituted 2-bromo-2-phenylacetonitriles. In this context, we took two more 2-bromo-2-phenylacetonitriles, namely 2-bromo-2-(4-chlorophenyl)acetonitrile and 2-(benzo-[*d*][1,3]dioxol-5-yl)-2-bromoacetonitrile to study the generality of this with respect to substituted 2-bromo-2-phenylacetonitrile.

Table 4. Reaction of ethyl 2-bromo-2-cyanoacetate with *N*-(phenylcarbamothioyl)benzamide in the presence of Et_3N



Entry	Substrate	Product	Time/min	Yield/%[a,b]
1		 **2q**	34	84

[a]Reactions performed in 10 mmol scale. Details of reaction conditions are shown in ref. 15. [b]Isolated yields.

The results are placed in Table 3. As shown in Table 3, the reactions with both the substituted 2-bromo-2-phenylacetonitriles reacted with various thiourea derivatives to form their corresponding thiazoline derivatives in good yields. Finally, we also used the present reaction conditions for the reaction of ethyl 2-bromo-2-cyanoacetate with *N*-(phenylcarbamothioyl)benzamide to obtain the desired 4-amino-2-iminothiazoline derivative in good yield. (Table 4).

In summary, we report an efficient methodology for the synthesis of 4-amino-2-iminothiazoline derivatives by using various 2-bromo-2-phenylacetonitriles and unsymmetrical thiourea derivatives as substrates. We have developed a simple, convenient, and effective method for easy synthesis of iminothiazoline derivatives under room temperature conditions. Present methodology has attractive features such as reduced reaction times and high yields. The simple procedure combined with ease of workup make this method economical, environmentaly benign, and a waste-free chemical process for the synthesis of iminothiazoline derivatives of biological importance.

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15 **General synthesis of 4-amino-2-iminothiazoline derivatives**: To 10 mmol of thiourea derivative in acetonitrile, was added triethylamine (10.50 equiv) and the mixture was stirred at room temperature (25–30 °C) for ten minutes then solution turned pale yellow. To that 10.10 mmol of 2-bromo-2-phenylacetonitrile (which was dissolved in 10 mL of acetonitrile) are added dropwise for ten minutes. After 15 min, yellow precipitate was observed. Solvent was concentrated under reduced pressure, solid material was filtered and washed with hexane to get rid off the excess of triethylamine. A yellow colored crystalline compound was observed. It was purified and characterized by the advanced spectroscopy.[17]

16 ***N*-(4-Amino-3,5-diphenyl-3*H*-thiazol-2-ylidine)benzamide (2a)**: mp: 78–80 °C; IR (KBr): 3220, 1670, 1598, 1560, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.0 (s, 2H, NH_2), 6.9–8.0 (m, 15H, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 95.3, 124.1, 126.7, 127.2, 129.8, 131.2, 133.7, 135.5, 136.8, 137.6, 167.0, 174.4, 178.5.; EIMS (*m*/*z*): 371.1.[17]

17 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html. Synthetic details of all new compounds with characterization.

