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One-pot sequential multicomponent route to 2,4-diaminothiazoles—a facile approach to bioactive agents for cancer therapeutics

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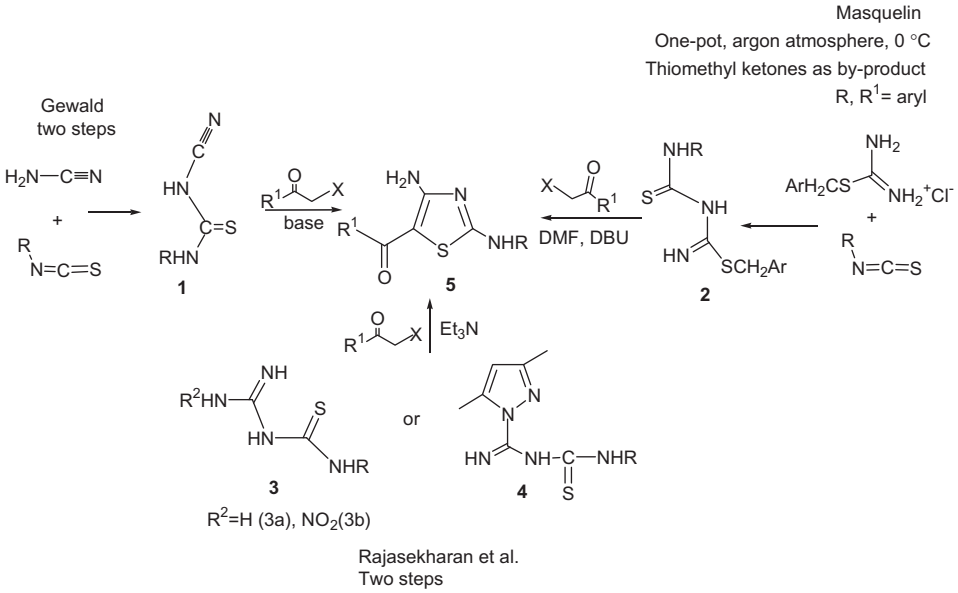
ABSTRACT

A facile one-pot sequential three-component route to 2,4-diaminothiazoles is reported. The new approach employs the mildest reaction conditions and commercially available reagents to generate diverse 2-alkyl/arylamino-4-amino-5-aroyl/heteroylthiazoles in short reaction times, good yield, and purity.

In the recent past, there has been intensified research in the discovery and synthesis of small molecules as bioactive agents for cancer therapeutics.[1] Among various thiazole containing anticancer drug candidates,[2] 2,4-diaminothiazoles are receiving significant



Scheme 1. Reported strategies for 2,4-diaminothiazole synthesis.

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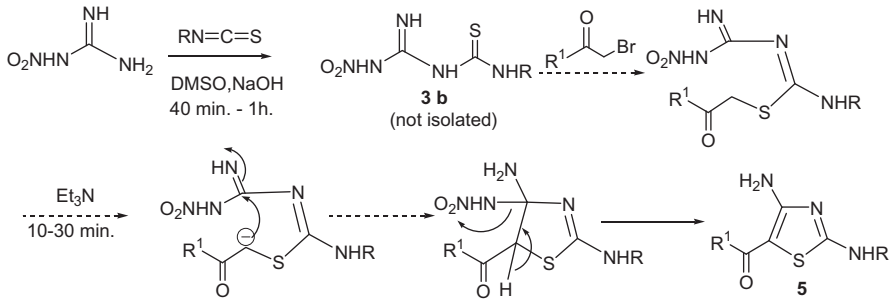


Scheme 2. One pot synthesis of 2,4-diaminothiazoles.

attention owing to their tubulin binding ability[3a] as well as cyclin dependent kinase (CDK) inhibitory activity.[3b,4] Thus the situation demands for simplified chemistry and facile one-pot protocols[5] amenable to combinatorial synthesis of diversely substituted 2, 4-diaminothiazoles which will generate libraries for structure–activity relationship (SAR) and clinical studies. The ring synthesis of 2,4-diaminothiazoles has received only scarce mention in the literature[6–8] (Scheme 1) and there is a further scope to improve upon the current methods. Interestingly, all the reported methods make use of the reaction between thiourea derivatives and an active methylene compound for thiazole ring construction.

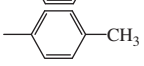
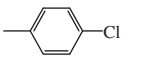
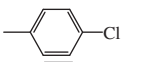
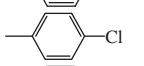
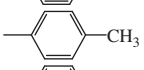
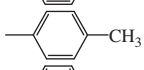
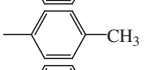
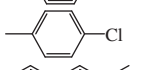
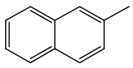
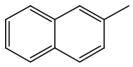
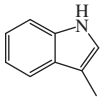
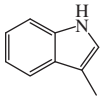
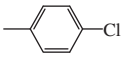
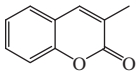
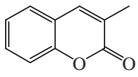
In Gewald method, cyanothioureas **1** accessed from cyanamide and isothiocyanates are utilized as four atom donor precursors. In their three-component strategy, Masquelin and Obrecht obtained thioureidothioureas **2**, as the condensation product of thiouronium salts and isothiocyanate. Rajasekharan's group, developed synthetic routes to diverse thioureas such as amidinothioureas[8] **3a**, nitroamidinothioureas[9] **3b,** and *N*-arylthiocarbamoylamidinopyrazoles[10] **4**. These thioureas are found to undergo base catalyzed cyclizations with α-haloketones to afford 2,4-diaminothiazoles **5** in [4+1] thiazole ring construction protocol. Gewald method follows Thorpe cyclization pathway whereas thioureidothioureas **2** eliminate thiomethyl ketones during cyclization. Reactions of **3** and **4** with α-haloketones are found to follow the S_N1 pathway leading to **5** by the elimination of R_2NH and 1-amidinopyrazole, respectively. We have also reported on a solid phase traceless method[11] which can be adapted to a combinatorial method to access these compounds.

However, during our synthetic expeditions to variously substituted aminothiazoles,[12] we have continuously refined the existing synthetic routes and have now discovered a simple and high yielding route to 4-amino-2-alkyl/arylamino-5-aroyl/heteroylthiazoles. In this letter, a new one-pot procedure for the fast and convenient synthesis of **5** is described. The reactions were carried out at room temperature using commercially available reagents to afford products in very good yield.

The proposed sequential three-component route employs nitroguanidine, isothiocyanates, and α-haloketones in a condensation followed by base catalyzed cyclization to afford 2,4-diaminothiazoles (Scheme 2). Of the various solvents tried, DMSO was found to be most suited, whereas DMF was the next preferred solvent. The optimized reaction, when carried out in DMSO was found to be complete (monitored by TLC) in 90 min to afford 2,4-diaminothiazoles as the sole product in yield >85% except for compound **5i** for which we obtained 78% yield.

During the optimization steps, we have isolated the condensation product of nitroguanidine and isothiocyanate and identified it as nitroamidinothiourea[9] which on the addition of α-haloketone underwent base catalyzed ring closure to 2,4-diaminothiazoles in an S_N1 pathway. The new one pot procedure is a tremendous improvement over the existing methods in terms of reaction conditions, product yield, and purity. In a typical example, nitroguanidine was stirred in DMSO containing an equiv sodium hydroxide to which an equimolar quantity of phenyl isothiocyanate was added and stirred. After further reaction, phenacyl bromide was added followed by Et_3N. Addition of Et_3N catalyzes the reaction as well as quenches the HBr evolved. After a total reaction period of 1 h, work-up gave 4-amino-5-benzoyl-2-phenylaminothiazole (**5a**) in 92% crude yield which after simple crystallization from a 1:1 mixture of methanol and benzene appeared as yellow shining crystals. Following a general procedure 12 diverse compounds (**5a–l**) were synthesized (Table 1) and characterized.[14]

Table 1
4-Amino-2-alkyl/arylamino-5-aroyl/heteroylthiazoles (**5a–l**)

Product **5**	R	R1	Yield[a] (%)
a			90
b			89
c			89
d			85
e			90
f			89
g*			90
h	CH_3		91
i[b]	CH_3		75
j	C_2H_5		83
k			90
l			82

[a] Yield of pure product.
[b] This product was obtained in only 78% yield whereas all others were obtained in >85% yield (crude).
* NMR data available in Ref. 13.

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Supplementary data

Supplementary data (detailed synthetic procedure and spectral characterizations of the compounds included) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.010.

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