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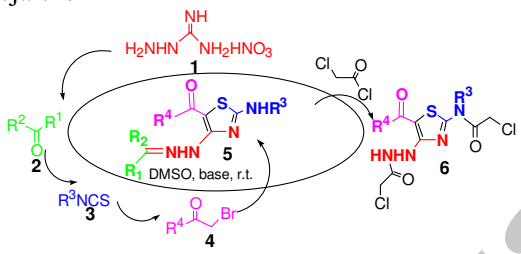

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One-pot four-component synthesis of 4-hydrazinothiazoles: novel scaffolds for drug discovery

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ABSTRACT

One pot ring synthesis of novel 4-hydrazinothiazoles through sequential four-component route employing carbonyl compounds, aminoguanidine, isothiocyanates and α-haloketones was accomplished under mild reaction conditions. Base-assisted eliminative aromatization in the [4+1] ring synthesis shed light into interesting leaving group propensities of amine versus hydrazine resulting in the exclusive formation of the title compounds with immense potential as scaffolds for drug discovery. Hydrazone deprotection was effected by acylation which subsequently provided new set of diacylated molecular systems with wider scope as chemical handles in the design of thiazolyl drug candidates.

Hydrazone libraries are currently gaining significance as potential drug discovery portal[1] and for dynamic combinatorial libraries (DCLs)[2] based on reversibility of hydrazone formations.[3]The functional diversity encompassed by the azomethine group elaborate the applicability of hydrazones in various fields including supramolecular chemistry,[4] organic frameworks,[5] hole-transporting materials[6] and dyes[7] among other applications. Our continued search for novel heterocyclic systems with promising bioactivities,[8] especially members of thiazole family, coupled with our interest in the development of combinatorial routes to access these systems[9] motivated us to design novel thiazole derivatives incorporating hydrazone substituent as potential lead molecules for drug discovery. We earlier reported on a plethora of C-N-C-S precursors, in solution phase,[9a,10] or anchored to solid support[9b] suitable for the [4+1] ring synthesis of substituted thiazoles. We were further motivated by the fact that despite numerous reports on the synthesis[11a] and wide spectrum of bioactivities exhibited by 2-hydrazinothiazoles **A**,[11b,12] their regioisomersviz; 4-hydrazinothiazoles **B** (Figure 1) have barely received mention in the literature. Thus it was of interest to design a synthetic route to these hitherto unreported molecular systems possessing a thiazole core with diverse substituents.

In this letter, we report a high-yielding, versatile and simple one pot method for the rapid synthesis of 4-hydrazinothiazoles **B** from carbonyl compounds, aminoguanidine, isothiocyanates and α-haloketones. It is noteworthy that our protocol allows diversity multiplication by varying carbonyl compounds, isothiocyanates and α-haloketones.

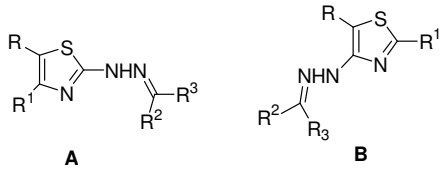
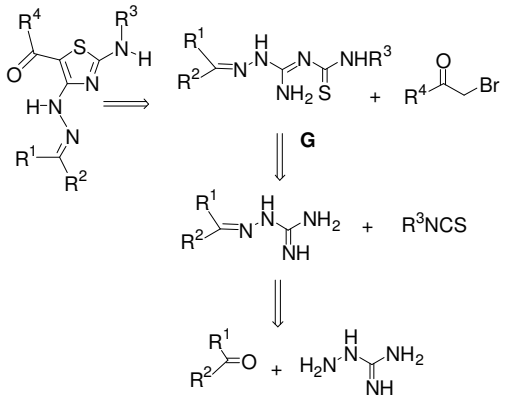


Figure 1. 2-Hydrazinothiazole **A** is reported widely in literature whereas 4-hydrazinothiazole **B** is hitherto unreported.

The versatility of the synthesis opens immense possibilities to explore reversibility of hydrazone formation for DCL by the judicious choice of carbonyl component.[3b] During our several trials for assessing the dynamicity of hydrazono linkage, we isolated yet another set of novel biacylated 4-hydrazinothiazoles and the results of the preliminary investigations are also discussed.

Following a retrosynthetic analysis (Scheme 1), we envisaged access to the title compounds through [4+1] ring synthesis similar to one we reported for 2,4-diaminothiazoles[13] by employing thiocarbamoylguanidines **G** as the C-N-C-S precursors. The access to **G** would require a sequential approach, if performed in a one-pot manner, owing to the binucleophilicity of aminoguanidine and we have previously reported on an optimized synthetic route.[10] However, unsymmetric substitution at the amidino carbon which suffers nucleophilic attack by the carbanion generated at active methylene carbon from α-haloketones during thiazole ring formation spawned further curiosity in studying hitherto unexplored cyclization pattern in these C-N-C-S systems.



Scheme 1. Retrosynthesis of 4-hydrazinothiazoles through [4+1] ring synthesis route.

The ring closure step is followed by eliminative aromatization leading to a thiazole derivative bearing a substituent at the 4th position of the ring, which largely is decided by the leaving group propensities of the competing species. In a hypothetical scenario (Figure 2), a plausible competition during the aromatization step may expel hydrazone (Path I) or ammonia (Path II) affording well known 2,4-diaminothiazoles[9,13] in the former case whereas latter would result in novel 4-hydrazinothiazoles **5**.

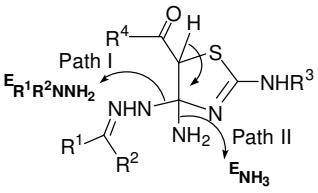
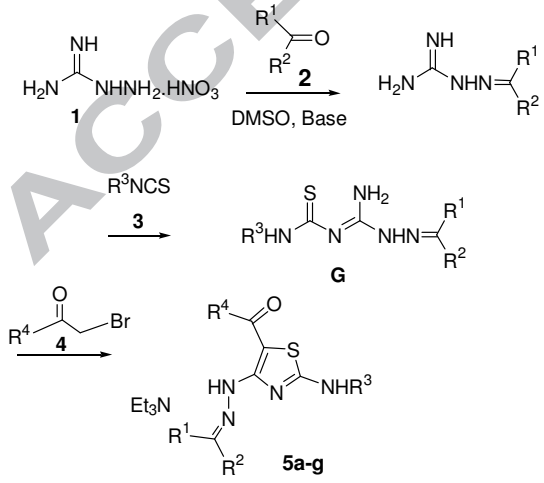


Figure 2. Plausible eliminations in the aromatization step.

We were curious about the cyclization pattern in these C-N-C-S precursors and in line with our interest in developing protocols for combinatorial library generation, planned for a one-pot procedure, notwithstanding the possibilities of ending up with mixture of products from competitive elimination. The scenario may further prove intricate since a possible configurational switching owing to the hydrazone bond can lead to E/Z isomers[14] in **5**.



Scheme 2. Sequential multicomponent route to afford 4-hydrazinothiazoles **5a-g**

To our great excitement, the optimized sequential four-followed by condensation of isothiocyanate **3** and finally base catalyzed cyclization with α-haloketones**4** afforded densely substituted 4-hydrazinothiazoles **5**, by elimination of ammonia, as the sole product (Scheme 2).[15] The versatility of the one-pot protocol was established by synthesizing compounds **5a-g** (Table 1) in excellent yield[16]and were completely characterized.[17]

Table 1. Novel 4-hydrazinothiazole derivatives **5a-g**accessed via Scheme 2

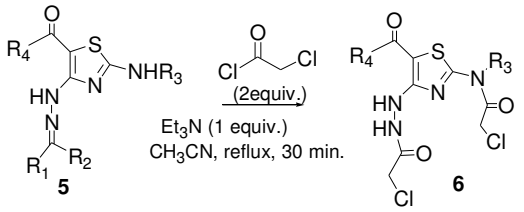
Entry	R^1	R^2	R^3	R^4	Yield(%)[a]
5a	CH_3	CH_3	C_6H_5	4-Cl C_6H_4	94
5b	CH_3	CH_3	C_6H_5	4-NO_2 C_6H_4	75
5c	CH_3	CH_3	C_6H_5	4-$OCH_3C_6H_4$	92
5d	CH_3	C_2H_5	C_6H_5	4-$OCH_3C_6H_4$	85
5e	-$(CH_2)_5$-		C_6H_5	4-Cl C_6H_4	95
5f	-$(CH_2)_5$-		C_6H_5	C_6H_5	95
5g	C_6H_5	H	C_6H_5	C_6H_5	95

[a]Isolated yield when the reaction was conducted in DMSO at r.t.

We employed acetone, 2-butanone, cyclohexanone and benzaldehye as carbonyl compounds in the optimized reaction conducted preferably in dipolar aprotic solvents like DMF or DMSO. The chemical diversity in the second and fifth positions of the thiazole ring was achieved by employing phenyl and substituted phenyl isothiocyanates as well as α-haloketones respectively. Simple work-up afforded **5a-g** as solid products which were purified by recrystallization. It is worth mentioning that our protocol encompasses vast scope for diversity multiplication by varying carbonyl compounds, isothiocyanates and α-haloketones all of which are commercially available with varied substituents.

Having achieved efficient ring synthesis of novel 4-hydrazinothiazoles bearing a terminal hydrazone bond, we were excited to explore further applications[17] of these hydrazone systems. Owing to the significance of dynamicity of the hydrazono linkage[2f-h,18] in DCL, we felt worth exploring reversibilites of hydrazone formations in our new molecular systems. The hydrazone linkage survived mild acid hydrolysis as well as exchange reaction with aminoguanidine salts and the starting compounds were recovered almost unreacted under our experimental conditions. This was quite expected and in agreement with the literature reports[3b] since electron withdrawing groups in the hydrazine nitrogen plays a key role in reversing the hydrazone formation equilibrium. We are further expanding our studies to impart structural features promoting the reversibility of hydrazone formation and results will be reported summarily.

Prompted by the interesting results on hydrazone bond stability, we next decided to probe the relative reactivities of nucleophilic centres in our title compounds. To this end, we performed acylations (Scheme 3) with chloroacetyl chloride in the presence of Et_3N[19] in CH_3CN under reflux conditions. After several trials, we accomplished deprotection of hydrazono substituent when **5**, chloroacetyl chloride and Et_3N were reacted in 1:2:1 ratio in refluxing CH_3CN for 30 min where upon the starting material was completely consumed and we isolated another class of novel thiazole derivatives **6** as the major product.



Scheme 3. Deprotection of **5** following acylation to afford **6**

Table 2. Diacylated 4-hydrazinothiazole derivatives **6a-c** accessed via Scheme 3

Entry	R^3	R^4	Yield(%)
6a	C_6H_5	4-Cl C_6H_4	70
6b	C_6H_5	4-$OCH_3C_6H_4$	65
6c	C_6H_5	C_6H_5	82

Subsequently we could establish the generality of the protocol by using differently substituted **5** to isolate products **6a-c**(Table 2) bearing two chloroacetyl substituents, one on terminal hydrazine N and the other on mono substituted amino N at the second position of the thiazole ring. These novel diacylated molecular systems are currently under active investigation to evaluate applications as chemical handles in drug development and in the design and development of thiazolyl azapeptides.

In summary, we have developed an efficient one-pot four-component ring synthesis method to access highly substituted novel 4-hydrazinothiazoles with potential applications in drug development. The [4+1] ring synthesis revealed interesting leaving group propensities of hydrazine vs amine in a competitive eliminative aromatization. Acylation employing chloroacetyl chloride facilitated deprotection of hydrazono linkage and subsequently provided yet another set of novel diacylated molecular systems bearing the thiazole core which may have a wider scope in the design of thiazolyl drugs and azapeptide analogues.

Supplementary Information

Detailed experimental procedures, characterization data of new compounds and copies of ^{1}H and ^{13}CNMR spectra are available as supporting information.

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Acknowledgments

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15. The use of unsymmetrical carbonyl compounds indicate a possibility of cis and trans isomers in some cases as identified by NMR spectroscopy (exemplified by ^{1}HNMR of **5d).** Details and spectra are provided in the supporting information.
16. General procedure for the synthesis of **5a-g**. To a stirred suspension of NaOH (10mmol) in DMSO, aminoguanidine nitrate followed by the ketone (10mmol each) was added. The mixture was stirred for 1h at room temperature and isothiocyanate (9mmol) was added and stirring continued for another 1h. Subsequently α-bromoketone (9mmol) was added followed by $E_{t3}N$ (10mmol), stirred for 15min. and worked up to afford solid products which were purified by recrystallization.
17. We have identified potential aurora kinase inhibitors from a library of these novel molecules and the results of molecular docking and cytotoxicity studies will appear elsewhere.
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