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Cyclocondensation of β-(aryl/heteroaryl)methylaminoenones with thionyl chloride: a facile general approach for the synthesis of 2,4-bis(het)aryl-5(het)aroylthiazoles

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ABSTRACT

An efficient, regioselective route to 2,4-bis(het)aryl-5(het)aroylthiazoles has been developed by cyclocondensation of thionyl chloride with novel β-(het)arylmethylaminoenones which are readily accessible by the reaction of (het)arylmethylamines with 1,3-bis(het)arylmonothio-1,3-diketones. The method allows entry to 2,4,5-trisubstituted thiazoles, with full control for the introduction of either a (het)aryl group at 2,4 positions or a (het)aroyl group at 5 position of the thiazole ring.

Thiazoles are among the most commonly encountered heterocycles of biological interest with many applications.[1] The thiazole ring is present in a large number of natural products; many of them have been isolated from marine organisms, and display significant biological activity such as cytotoxic, antifungal, antituberculosis, enzyme inhibitors, and peripheral analgesics.[1] This heterocyclic system is found in several marketed drugs and occupies a prominent position in drug development[2] for the treatment of inflammation, hypertension, bacterial and HIV infection, herbicides, and fungicides.[3] Also, some thiazole derivatives have found application as liquid crystals for ferroelectric display[4] and as cosmetic sunscreens.[5]

Among the various methods available for substituted thiazoles,[1] Hantzsch thiazole synthesis[6] (or its modified versions)[7] has proven to be a powerful method for the synthesis of 2,4,5-substituted thiazoles, involving condensation of α-haloketones (or its variant) with thioamides. Other methods include reaction of α-aminonitriles with CS_2, COS, isothiocyanates, and dithiocarboxylic acids,[8] and thionationcyclization of α-acylaminoketones (or related precursors) with various thionation reagents such as P_2S_5, H_2S, Lawesson, or Belleau's reagent.[9] Recently 2,4,5-trisubstituted thiazoles have also been synthesized through palladium catalyzed cross-coupling reactions and C—H arylation.[10] Despite these advances, more flexible, general regioselective routes for functionalized thiazoles are still needed.

We have recently reported the synthesis and reaction of 1,3-monothiodiketones **1**,[11] a new class of three carbon 1,3-bielectrophilic precursors, which have not been much explored. During the course of these studies, with a view to examine further synthetic applications of these 1,3-bis(het)arylmonothiodiketones **1**, we have reacted these intermediates with various (het)arylmethyl amines and subjected the resulting enaminones **2** to cyclocondensation with thionyl chloride, furnishing the corresponding 2,4-diaryl/heteroaryl-5-acyl thiazoles of the general structure **3** in moderate to good yields. The results of these studies have been reported in this Letter.

The desired enaminones **2a–j** carrying a β-(aryl/heteroaryl)methylamino group were obtained in excellent yields in highly regioselective manner, by condensation of the corresponding 1,3-monothiodiketones **1a–j** with the appropriate (het)arylmethylamines **4** in ethanol at room temperature in the presence of acid catalyst (Scheme 2). Enaminone **2a** was selected as a model substrate for optimizing the reaction conditions for the formation of thiazole **3a** in the presence of various bases and solvents (Table 1, Scheme 1). Thus treatment of **2a** with thionyl chloride in the presence of pyridine, both as base and solvent at 0 °C under the conditions described earlier,[12] afforded the desired 4-(4-methoxyphenyl)-2-(4-methylphenyl)-5-benzoylthiazole **3a** only in 15% yield (Table 1, entry 1). Similarly, thiazole **3a** was obtained in low yield, when the reaction was conducted in dichloromethane as solvent in the presence of pyridine as base (Table 1, entry 2).

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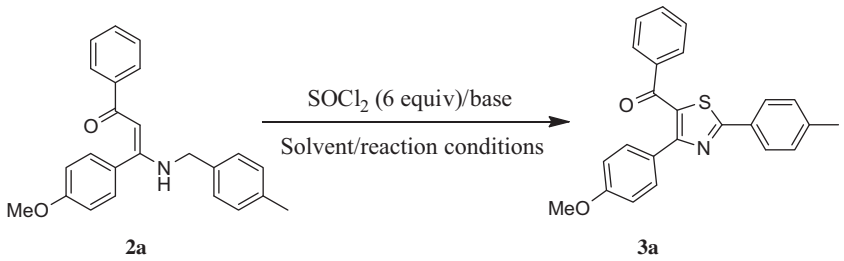


Scheme 1. Synthesis of (4-(4-methoxyphenyl)-2-p-tolylthiazol-5-yl)(phenyl)methanone **3a**.

However, a dramatic increase in the yield (65%) of thiazole **3a** was observed when 4-(dimethylamino)pyridine (DMAP) was used as base instead of pyridine under similar conditions (Table 1, entry 3) probably due to enhanced base strength of DMAP. Use of other bases such as DBU, triethylamine, afforded thiazole **3a** in lower yields (Table 1, entries 4 and 5), whereas, enaminone **2a** was recovered unchanged, when K_2CO_3 was used as base (entry 6). Dichloromethane was found to be the best solvent with DMAP as base for this reaction and lower yields of thiazole **3a** were obtained by use of other solvents such as THF, acetonitrile, acetone, or dichloroethane even after prolonged reaction time. Attempts to further improve the yield of **3a** by varying the reaction temperature or time were not successful yielding only intractable reaction mixture.

With the optimized reaction conditions in hand, we next examined the generality and scope of the reaction for the synthesis of other substituted thiazoles **3b–j** from the respective enamines **2b–j** as shown in Table 2. Thus enaminones **2b**,**c** derived from 3,4-methylenedioxy- and 3-(trifluoromethyl)benzylamines also underwent cyclocondensation with thionyl chloride under these conditions, yielding the corresponding 2,4-diaryl-5-aroylthiazoles **3b**,**c** in 58% and 55% yields respectively (Table 2, entries 2 and 3). Similarly, enaminones **2d–f** carrying a (het)aryl group such as 3-indolyl- or 3-pyridyl moieties also furnished the (het)aryl substituted thiazoles **3d–f**, although in moderate yields (Table 2, entries 4–6). On the other hand, the thiazoles **3g**,**h**, bearing 2-furyl/thienyl and 2-furoyl/2-thiophenecarbonyl groups at 4 and 5 positions were obtained in higher yields from the respective enaminones **2g**,**h** under these conditions. (Table 2, entries 7 and 8). Enaminone **2i** derived from (2-thienyl)methylamine also furnished 4,5-disubstituted 2-(2-thienyl) thiazole **3i** in 54% yield under similar conditions (Table 2, entry 9). Finally, it was possible to install three different (het)aryl groups at various positions of thiazole **3j** using this protocol, by subjecting enaminone **2j**, derived from 3-(picolyl) amine to cyclocondensation under these conditions (Table 2, entry 10). Enaminone **2k**, from 2-(furyl)methylamine failed to give any thiazole **3k** yielding only unchanged enaminone **2k** (Table 2, entry 11). At this stage, it is not possible to give any rational explanation for the inertness of enaminone **2k** under the described reaction conditions.

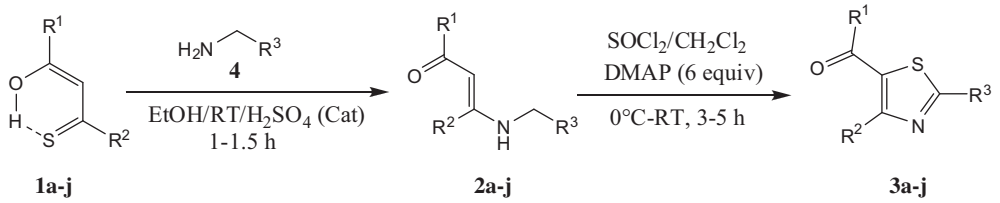
The probable mechanism for the formation of thiazoles **2** appears to be similar to that suggested earlier,[12] and is depicted in Scheme 3. Thus, the nucleophilic attack of enaminone **2** on thionyl chloride, followed by elimination of HCl in intermediate **5** furnishes sulfene intermediate **6**, which on subsequent deprotonation and intramolecular cyclization of the resulting anion **7** affords thiazoline S-oxide anion **8**. Further reaction of **8** with another molecule of thionyl chloride affords thiazoles **3** by deoxygenation through a Pummerer intermediate **9** (Scheme 3).

In conclusion, we have reported an efficient regioselective route to β-(het)arylmethylamino enones **2** from readily available 1,3-bis(het)aryl-1,3-monothiodiketones **1** and utilized these enaminones **2**, to develop a straightforward general approach for diversity oriented synthesis of 2,4-bis(het)aryl-5-(het)aroyl thiazoles **3**. The strategy reported herein allows us a novel entry to 2,4,5-trisubstituted thiazoles with full control over substitution at the 2- and 4- and 5-positions. Although the yields of thiazoles are modest to good, the route offers a direct access to a large number of diverse new thiazoles based on pharmaceutically relevant structures, which would otherwise be considerably more difficult to prepare by alternative routes. In addition, this method offers a facile regioselective entry to 5-(het)aroylthiazoles, thus overcoming the limitations of Hantz type condensation,[13] in which the mixture of regioisomeric thiazoles are formed with unsymmetrical α-halo1,3-diketones.[14]

Table 1
Optimization of reaction conditions for the formation of thiazole **3a**

Entry	Base[a]	Solvent	Time (h)	Yield (**3a**) (%)
1	Pyridine	Pyridine	3	15
2	Pyridine	CH_2Cl_2	3	25
3	DMAP	CH_2Cl_2	3	65
4	DBU	CH_2Cl_2	5	32
5	Et_3N	CH_2Cl_2	7	10
6	K_2CO_3	CH_2Cl_2	10	—[b]

[a] 6 equiv of base.
[b] Compound **2a** was recovered unchanged.



Scheme 2. Synthesis of enaminones **2a–j** from **1a–j** and thiazoles **3a–j**.

Table 2
Synthesis of 2,4-bis(het)aryl-5-(het)aroyl thiazoles **3a–j** from enaminones **2a–j**

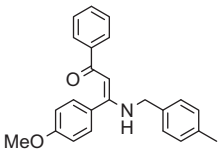
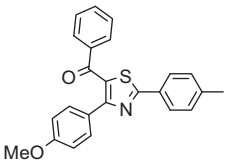
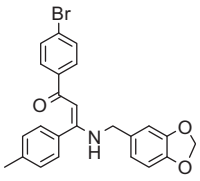
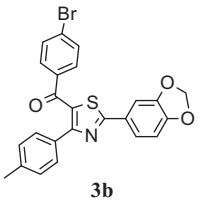
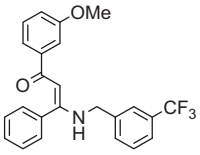
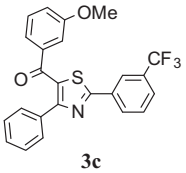
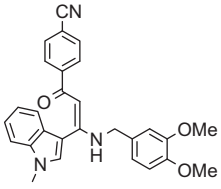
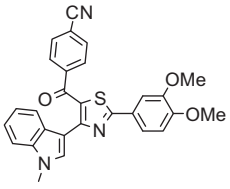
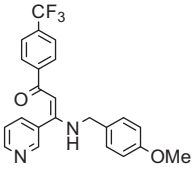
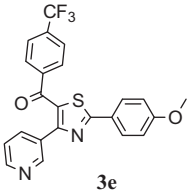
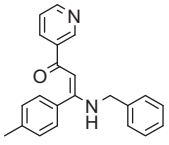
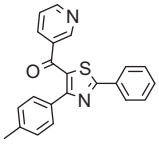
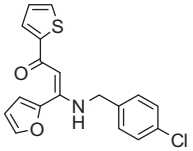
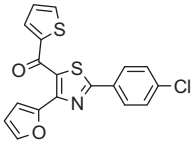
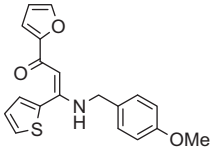
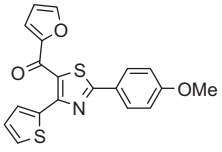
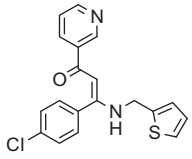
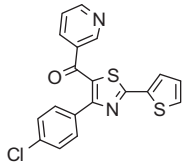
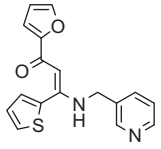
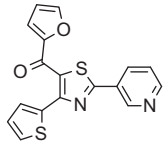
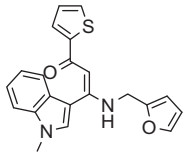
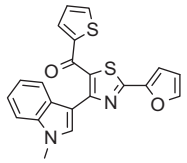
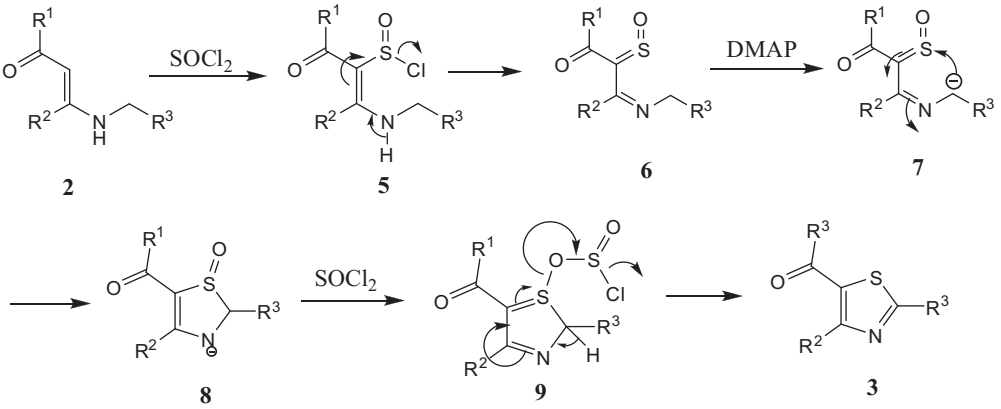
Entry	**2**	Yield **2** (%)	**3**	Yield **3** (%)
1	 **2a**	85	 **3a**	65
2	 **2b**	79	 **3b**	58
3	 **2c**	82	 **3c**	55
4	 **2d**	58	 **3d**	48
5	 **2e**	70	 **3e**	56
6	 **2f**	72	 **3f**	53
7	 **2g**	78	 **3g**	68
8	 **2h**	80	 **3h**	75

Table 2 (*continued*)

Entry	2	Yield **2** (%)	3	Yield **3** (%)
9	 **2i**	75	 **3i**	54
10	 **2j**	72	 **3j**	45
11	 **2k**	55	 **3k**	0



Scheme 3. Probable mechanism for the formation of thiazoles **3**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.079.

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