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A facile and eco-friendly synthesis of diarylthiazoles and diarylimidazoles in water

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ABSTRACT

A simple, efficient and high yielding greener protocol for the synthesis of substituted thiazoles and imidazoles is described that utilizes the reaction of readily available α-tosyloxy ketones with variety of thioamides/amidines in water.

Thiazoles and imidazoles are important heterocycles known for their broad spectrum of biological activities.[1,2] Natural and synthetic molecules containing thiazole scaffold play a significant role in pharmaceutical industry due to their anti-inflammatory,[3] anti-HIV,[4] anti-bacterial[5], and anti-schizophrenia[6] properties. The aminothiazoles are ligands for estrogen receptors[7] and studied for their anti-cancer activity.[8] This structural unit is a part of many agro-chemicals[9] and natural products such as vitamin B_1 (thiamine). Cystothiazole and its analogues, isolated from *Mycobacterium* culture broth of *Cystobacter fuscus*, show anti-bacterial activity. Mycothiazole, isolated from the Indo-Pacific sponge *Spongia mycofijiensis*, displays anthelmintic activity and selective cytotoxicity against lung cancer,[10] some indole-based secondary metabolites containing thiazole nucleus are known to display interesting anti-cancer activity.[11] Similarly, analogues bearing imidazole moiety is an active pharmacophore in several natural and synthetic drug molecules. Diarylimidazoles are well documented for their wide range of biological activities[12–14] and imidazole containing natural products such as topsentine, nortopsentine, and analogues show prominent anticancer activity.[15]

In view of immense biological significance of these five-membered azoles, many synthetic protocols have been reported. However, in recent years the key constraints for the synthetic chemists are the use of hazardous solvents, multi-step protocols, generation of unwanted side-products, and the use of moisture sensitive and expensive reagents.[16] To overcome these problems and to find new alternatives for simple and environmentally benign protocols, chemists have adopted water as solvent of choice in the organic synthesis. Usage of water addresses the several concerns of green chemistry such as easy availability, safe handling, simple workups and cost effective for small and bulk scale process industries. Water due to its high hydrophobic nature can enhance the rates and affect the selectivity of various organic transformations.[17] In the recent years a variety of organic transformations such as aldol reaction, allylation reaction, Diels–Alder reaction, Michael reaction, Mannich-type reaction, Henry reaction, and Pd catalyzed coupling reactions have been reported in aqueous media.[17,18] In continuation of our efforts for the development of novel and eco-friendly protocols to synthesize biologically active molecules, we have explored solvent-free synthesis, the use of alternative solvent media such as PEG-400, ionic liquids, aqueous media, polymer supported sulfonic acid reagents and microwave-assisted organic reactions.[19]

In this Letter, we report a facile synthesis of various thiazoles and imidazoles in water. There are several synthetic routes to construct diarylthiazoles and diarylimidazoles. Hantzsch synthesis involving the reaction of α-haloketones with various thioamides is the most prominent method of choice,[20] however, this method suffers from longer reaction times, harsh reaction conditions and the use of lachrymatory reagents. Subsequent efforts to improve efficiency of this method entails the use of solvents such as DMF, 1,4-dioxane and chlorinated solvents.[21] Some recent reports have focused on the use of alternative solvents such as PEG-400 and ionic liquids.[22] Many improved results have been reported for the

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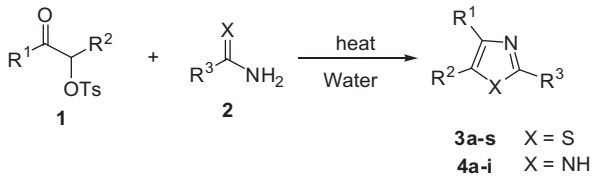

Scheme 1. Synthesis of thiazoles **3** and imidazoles **4**.

Table 1
Yields of diarylazoles **3a** and **4a** in various solvents[a]

Entry	Solvent	**3a**[b] (%)	**4a**[b] (%)
1	EtOH	47	23
2	MeOH	40	18
3	DMF	15	10
4	CH_3CN	27	No product
5	THF	18	30
6	Xylene	23	No product
7	Toluene	20	No product
8	$CHCl_3$	30	55
9	CH_2Cl_2	35	25
10	Distilled water	87	70
11	Tap water	84	68

[a] Reaction conditions: α-tosyloxyacetophenone (1 mmol), thiobenzamide/benzamidine (1 mmol) and solvent (0.5 mL); **3a** stirred at 60 °C for 5 h/**4a** stirred at 80 °C for 3 h.
[b] Isolated yields.

synthesis of thiazoles using KF-10 clay,[23] ammonium 12-molybdophosphate,[24] β-cyclodextrin,[25] and microwave-assisted synthesis.[26] Despite these reports, there is a vast scope to develop eco-friendly alternatives that preclude the use of any catalysts or hazardous solvents, high temperatures and improving the yields.

α-Tosyloxyketones were prepared from enolizable ketones using hydroxyl(tosyloxy)iodobenzene as reported in literature.[27] α-Tosyloxyketones are one of the versatile intermediates which have replaced highly toxic and lachrymatory α-haloketones to prepare variety of heterocycles.[28,29] Thioamides were synthesized from the reaction of corresponding arylnitiriles with NaSH in DMF.[30] Our initial attempts involving the reaction of α-tosyloxy acetophenone **1** with thiobenzamide in water at ambient temperature were unsuccessful to produce desired product and hence, the reaction was investigated at various temperatures. We found 60 °C was optimum temperature and affords desired product in good yield (Scheme 1). Pure products were isolated by simple filtration or recrystallization of the ensuing products. To understand the unprecedented role of water as a solvent and reaction promoter, we have conducted the synthesis of diarylthiazoles in various organic solvents. A comparative study was made using organic solvents, such as polar–protic (ethanol and methanol) and polar–aprotic (acetonitrile, THF and DMF) which has the drawbacks such as prolonged reaction times, incompletion of the reaction and resulted in poor yields (Table 1). In nonpolar solvents toluene and xylene reaction needs higher temperatures and yields are moderate. Results were not satisfactory in chlorinated solvents such as $CHCl_3$ and CH_2Cl_2. Further, a model reaction was studied at our optimized reaction conditions and results were compared with the water and organic solvents (Table 1). Encouraged by the favorable results in water, the scope of the reaction was investigated by reacting a variety of α-tosyloxyketones **1** having electron-withdrawing and electron-donating groups, and aryl and heteroaryl thioamides **2** to generate a library of disubstituted thiazoles **3** (Table 2).[31] In the case of heteroaryl thioamides yields were less when compared with aryl systems. In several aspects usage of water is advantageous, as it is environmentally benign and due to its high hydrogen bonding capacity it can stabilize the intermediates formed in Hantzsch thiazole synthesis to promote the reaction (Fig. 1).

Synthesis of imidazoles is often reported from the reaction of glyoxal with a variety of aldehydes in the presence of ammonium acetate.[32] Synthesis of imidazole ring is also achievable by reacting α-haloketones with amidines in organic solvents such as chloroform, DMF, acetonitrile, and alcohols.[33]

Table 2
Synthesis of diarylthiazoles **3** and diarylimidazoles **4**

Compound	R^1	R^2	R^3	Yield[a] (%)	Time (h)	Mp (°C)
3a	C_6H_5	H	C_6H_5	87	5.0	89–90 (90–91)[24]
3b	C_6H_5	H	4-ClC_6H_4	90	6.0	104 (104–105)[25]
3c	C_6H_5	H	NH_2	92	1.0	148–149 (149–150)[24]
3d	C_6H_5	H	CH_3	82	5.0	64–65 (64)[30]
3e	C_6H_5	H	4-$OCH_3C_6H_4$	80	4.0	99–100 (98–99)[25]
3f	C_6H_5	H	3-Indolyl	70	4.0	278–279
3g	C_6H_5	H	4-Pyridyl	65	5.0	108–109
3h	C_6H_5	H	1-Methyl-3-indolyl	85	4.0	90–91
3i	CH_3	$COCH_3$	C_6H_5	85	5.0	68–70 (70–71)[25]
3j	CH_3	$COCH_3$	4-ClC_6H_4	90	3.0	113–114 (114)[25]
3k	CH_3	$COCH_3$	4-$OCH_3C_6H_4$	90	3.0	89 (88–89)[25]
3l	4-$OCH_3C_6H_4$	H	C_6H_5	88	3.0	126–127 (127–129)[24]
3m	4-$OCH_3C_6H_4$	H	4-ClC_6H_4	93	3.0	140–141(139–140)[25]
3n	4-$OCH_3C_6H_4$	H	NH_2	80	4.0	205–206 (206–208)[24]
3o	4-ClC_6H_4	H	C_6H_5	85	3.0	130–132 (131–132)[24]
3p	4-ClC_6H_4	H	4-ClC_6H_4	90	4.0	144–145 (145)[25]
3q	4-ClC_6H_4	H	3-Indolyl	87	4.0	248–249
3r	1-$PhSO_2$-3-indolyl	H	C_6H_5	75	6.0	182–184
3s	1-$PhSO_2$-3-indolyl	H	1-Methyl-3-indolyl	86	5.0	156–158
4a	C_6H_5	H	C_6H_5	70	3.0	166–167 (168)[24]
4b	C_6H_5	H	4-ClC_6H_4	65	3.5	264–265 (263–265)[29]
4c	C_6H_5	H	4-Pyridyl	65	2.5	238–240 (237–240)[29]
4d	4-ClC_6H_4	H	C_6H_5	70	3.0	277–279 (278–279)[29]
4e	4-ClC_6H_4	H	4-ClC_6H_4	63	3.0	190–191
4f	4-ClC_6H_4	H	4-Pyridyl	55	2.0	227–229
4g	4-$OCH_3C_6H_4$	H	4-ClC_6H_4	55	3.0	233–235
4h	4-$OCH_3C_6H_4$	H	4-Pyridyl	60	2.5	246–248
4i	4-$OCH_3C_6H_4$	H	C_6H_5	50	3.5	177–179 (178–179)[29]

[a] Isolated yields.

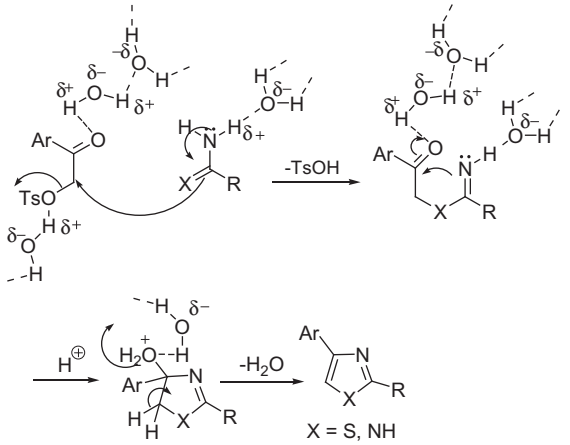

Figure 1. Proposed water mediated construction of diarylazoles **3** and **4**.

Reported protocols are plagued by poor yields and requirements of higher temperatures. We report the formation of diarylimidazoles **4** by reacting α-tosyloxyketones **1** with amidines **2** in benign solvent, water. Our initial attempts to achieve this condensation reaction in aqueous medium were unsuccessful at room temperature. However, reactions proceeded smoothly at 80 °C and further increase of temperature resulted only in the formation of undesired products. Syntheses of diarylimidazoles were also investigated in different organic solvents, such as THF, $CHCl_3$, and DMF (Table 1). Under similar reaction conditions in organic solvents poor yields and prolonged reaction timings were observed. We have synthesized a library of diarylimidazoles **4** (Table 2) using the optimized reaction conditions. Reaction of pyridylamidine with α-tosyloxyketones having electron-donating groups resulted in lower yields. Over all, yields are lower in case of diarylimidazoles as compared to diarylthiazoles, possibly due to the enhanced nucleophilicity of sulfur in thioamides when compared to nitrogen amidines. All the synthesized compounds were characterized by IR, 1H NMR and Mass spectral data.[31]

In conclusion, we have developed a simple and greener approach for the synthesis of bioactive molecules, diarylthiazoles and diarylimidazoles in good yields. Protocol is highly efficient and facile in water as solvent and reaction promoter. The advantages of the reaction conditions include no metal reagents, avoidance of toxic, volatile, and corrosive organic solvents and the relative ease of safe experimental procedures. This method is a useful and attractive strategy to generate a diverse array of bioactive thiazoles and imidazoles under eco-friendly conditions.

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31. *General experimental procedure:* To a stirred solution of aryl thioamide or amidine (1 mmol) in 5 mL distilled water was added α-tosyloxyketone (1 mmol) and the reaction mixture stirred at 60 °C or 80 °C till completion. Progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, product was readily filtered and recrystallized from ethanol (**3a–k**, **3p–o** and **4a–e**). In some cases (**3l–m** and **4f–i**) product was extracted with dichloromethane (25 mL), washed with brine (25 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and distilled off in vacuum. The residue so obtained was purified by column chromatography on silica gel (100–200 mesh) (EtOAc/Hexane) to give pure product. *Analytical data for some representative compounds*. **3f**: Off-white solid; IR (KBr): 3132, 1595;1539, 1435, 1340, 734, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.80 (s, 1H), 8.34–8.31 (m, 1H), 8.16 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 8.03, 1H), 7.94 (s, 1H), 7.52–7.47 (m, 3H), 7.26–7.21 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H); MS (FAB) m/z calculated for $C_{17}H_{12}N_2S$ $(M)^+$ 276.07, observed 276.30. **3h**: Pale yellow solid; IR (KBr): 3032, 1623, 1580, 1484, 1325, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.97–7.94 (m, 2H), 7.74 (s, 1H), 7.40–7.36 (m, 3H), 7.26–7.16 (m, 4H), 3.74 (s, 3H); MS (FAB) m/z calculated for $C_{18}H_{14}N_2S$ $(M+H)^+$ 291.10, observed 291.0. **3q**: White solid; IR (KBr): 3145, 1650, 1426, 1380, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.79 (s, 1H), 8.31–8.33 (m, 1H), 8.16 (d, J = 2.8 Hz, 1H), 8.13–8.09 (m, 1H), 8.00 (s, 1H), 7.59–7.47 (m, 2H), 7.27–7.21 (m, 2H), 7.12 (d, J = 7.8 Hz, 2H); MS (FAB) m/z calculated for $C_{17}H_{11}ClN_2S$ $(M)^+$ 310.03, observed 310.06. **3r**: Off-white solid; IR (KBr) 3130, 1625, 1460, 1176, 979, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.98–8.01 (m, 3H), 7.87 (d, J = 3.4 Hz, 1H), 7.89 (s, 1H), 7.48–7.38 (m, 5H), 7.37 (s, 1H), 7.32–7.28 (m, 3H); MS (FAB) m/z calculated for $C_{23}H_{16}N_2O_2S_2$ $(M+Na)^+$ 439.05, observed 439.1. **4f**: White solid; IR (KBr) 3213, 1607, 1534, 1488, 1315, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06–8.01 (m, 2H), 7.94 (d, J = 8.7 Hz, 2H), 7.47–7.40 (m, 4H), 7.34–7.30 (m, 2H), MS (FAB) m/z calculated for $C_{14}H_{10}ClN_3$ $(M+H)^+$ 256.06, observed 255.8. **4g**:

White solid; IR (KBr) 3195, 1660, 1520, 1465, 1245, 827, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.42–7.28 (m, 3H), 7.24 (s, 1H), 6.92 (d, J = 8.20 Hz, 2H), 3.75 (m, 3H); MS (FAB) m/z calculated for $C_{16}H_{13}ClN_2O$ $(M+H)^+$ 285.08, observed 285.08. **4h**: White solid; (KBr) 3150, 1660, 1580, 1470, 1280, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 9.6 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 7.41–7.36 (m, 3H), 7.27 (s, 1H), 6.90 (d, J = 9.2 Hz, 2H), 3.79 (s, 3H); MS (FAB) m/z calculated for $C_{15}H_{13}N_3O$ $(M+H)^+$ 252.1, observed 252.4.

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