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Highly Efficient Green Protocol for the Synthesis of 2-amino-4-arylthiazoles

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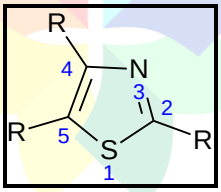
Abstract: A highly efficient and facile method has been described for the synthesis of substituted 2-aminothiazoles in water without any added catalyst or co-organic solvent. The reaction was carried out at ambient temperature and the products were obtained in excellent isolated yields.

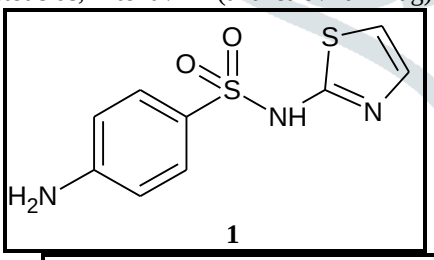
***Index Terms* – α chloroacetophenone, 2-amino-4-arylthiazole, thiourea.**

I. INTRODUCTION

Thiazole is one of the most imperative classes of aromatic five-membered heterocycle. It was first described by Hantzsch and Weber in 1887. These heterocycles having sulfur and nitrogen heteroatoms at positions 1 and 3, respectively is present in many of the natural products. Thiazole or 1-3 azole is a clear monochrome to light yellow flammable liquid. It has pyridine like smell. Number of derivatives of thiazoles has been prepared by adding substituents at 2, 4 and 5 positions. The structure of thiazole can be written as



Thiazoles and their derivatives show various biological activities like fungicidal, sedatives, anesthetics, bactericidal, anti-inflammatory etc. The thiazole ring is a part of many potent biologically active molecules such as sulphathiazole **1** (antimicrobial drug), Tiazofurin **2** (antineoplastics drug), vitamin B_1 **3** (serve as an electron sink), and its coenzyme form is important for the decarboxylation of α-ketoacids, Ritonavir **4** (antiretroviral Drug).



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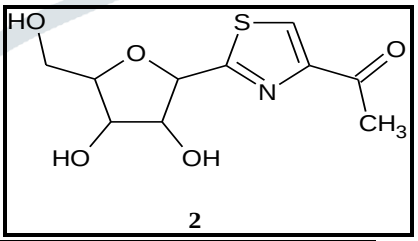

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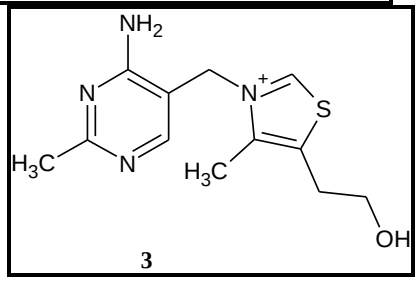

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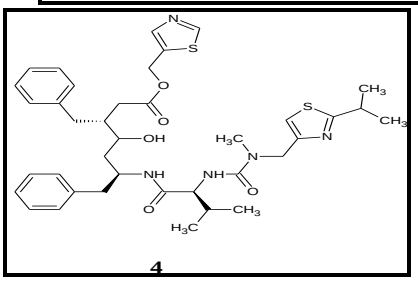

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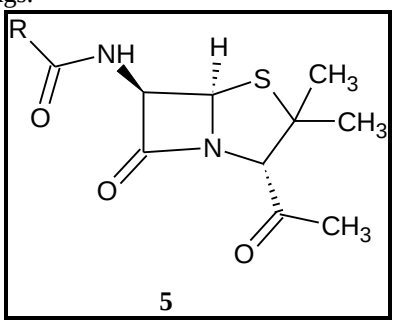
Among pharmacologically important heterocyclic compounds, thiazole and its derivative 2-aminothiazole have been well known in pharmaceutical chemistry because of their wide spectrum of biological activities.[1,2] Their presence in naturally occurring compounds e. g. antibiotics like penicillin **5,** cephalosporin, micrococcin, tigmonam, Aztreonam (monobactum antibiotic), Amiphenazole **6** (respiratory stimulant), etc. 2-aminothiazole derivatives, having various functional groups at carbon and nitrogen atom in the thiazole ring are important molecules for medicinal and biological useful heterocycles. 2-aminothiazoles are also found to have applications as herbicides and fungicides.[3] 2-substituted-amino-4-arylthiazole**,** S-derivatives of triazolyl thiazole**,** (2-

aminothiazol-4-yl)-methylester**,** thiazolidinoes**,** modified phenylthiazole derivative**,** etc has good antitubercular activity and seems to be future anti-tubercular drugs.[1,4-7]



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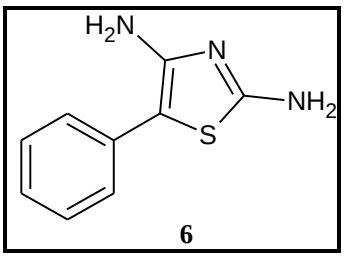

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In recent years, the interest in synthesis of biologically active heterocyclic compounds is greatly increased. The heterocycles containing nitrogen and sulfur atom has acquired more importance in medicinal chemistry. The thiazole ring is a part of many potent biologically active molecules such as Sulfathiazole (Antimicrobial drug), Tiazofurin (Antineoplastics drug), and Ritonavir (Antiretroviral drug). This class of compounds has various medicinal applications like antibiotics[8], photo sensitizers[9], antibacterial[10], antitubercular[11], antifungal[12], anti-HIV[13], and anti-inflammatory[14]. Some thiazole derivatives have found applications in drug development for the treatment of allergies[15], hypertension[16], and schizophrenia[17]. Amino thiazoles are also used as ligands of estrogen receptors[18]. Several methods for the synthesis of thiazole and its derivatives were developed by Hantzsch, Tchernic, Cook Helborn, Gabriel, and other groups[19]. Other methods developed by different workers, from α-haloketone and thioamide using β-cyclodextrin as catalyst[20], by the reaction of acetophenone with thiourea using Br_2/I_2 as catalyst[21], from α-bromoketone, primary amine and phenylisothiocynate in presence of catalytic amount of triethylamine[22], 2-aminothiazole derivatives were synthesized from α-bromoketone, thiourea catalytic amount of ammonium chloride[23], ring expansion of 1-arylmethyl-2-(thiocynatomethyl)aziridine with an acyl chloride in presence of $TiCl_4$[24].

However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedures, polar/volatile/hazardous organic solvents, and often expensive catalysts. These processes also generate waste-containing solvent and catalysts, which have to be recovered, treated, and disposed off. The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvent but also because water exhibits unique reactivity and selectivity, which is different from those obtained in conventional organic solvents. Thus, elements of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[25] The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding.[26] Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry. Our recent results obtained during the synthesis of benzodiazepines promoted by water prompted us to investigate the heterocyclization reaction for the synthesis of biologically active heterocycles using water as a solvent. In continuation to our research devoted to development of green organic processes for the synthesis of biologically active heterocycles, herein we report an efficient and facile method for the synthesis of 2-aminothiazoles in water at ambient temperature

II. Material and Methods

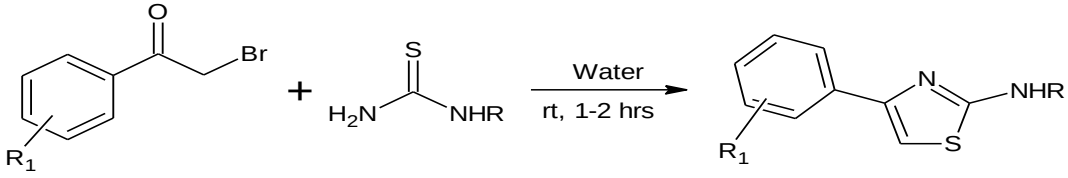
All the chemicals were of analytical grade. The melting points were determined by open capillary methods and are uncorrected. Synthesized compounds were purified by simple crystallization. The purity of compound was checked by thin-layer chromatography. The IR spectra were recorded on "Shimadzu" IR spectrophotometer using KBr pallet. 1HNMR spectra were recorded on "Avance-300" spectrometer using CDCl3 as solvent and tetramethylsilane as internal standard. Mass spectra were recorded in electron impact mode.

General Procedure for the synthesis of Thiazoles

A mixture of phenacyl bromide 1 (1 mmol) and thiourea 2 (1.1 mmol) was stirred in water (5 mL) at room temperature under vigorous magnetic stirring for the specified time as mentioned in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted using ethyl acetate (2×15 mL). The organic layer was separated from aqueous layer. The combined organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to obtain the crude solid product. The crude product was further purified by column chromatography using ethyl acetate /petroleum ether as eluent to afford the pure product 3.

III. Result and Discussion

When phenacyl bromide was treated with thiourea in water at room temperature, to our surprise, the reaction occurred affording 4-phenylthiazol-2-amine (Scheme). These compounds were characterized by spectral data.



1 2 3

Scheme

Table 1.

Sr. No	Entry	R1	R	Yield (%)a	M. P. (oC)b	Reaction Time (Hrs.)
01	T1	3-CH3, 5-I	-H	90	160	1.5
02	T2	5-CH3, 3-I	-H	87	142	2.0
03	T3	4-CH3, 3,5-I	-H	85	150	2.2
04	T4	5-Cl, 3-I	-H	87	175	2.7
05	T5	3-CH3, 5-I	-CH3	91	132	1.7
06	T6	5-CH3, 3-I	-CH3	86	122	2.4
07	T7	4-CH3, 3,5-I	-CH3	84	118	2.5
08	T8	5-Cl, 3-I	-CH3	87	129	3.2
09	T9	3-CH3, 5-I	-C6H5	92	112	1.6
10	T10	5-CH3, 3-I	-C6H5	87	135	2.1
11	T11	4-CH3, 3,5-I	-C6H5	83	130	2.4
12	T12	5-Cl, 3-I	-C6H5	82	121	2.9
13	T13	3-CH3, 5-I	-C10H7	89	116	2.0
14	T14	5-CH3, 3-I	-C10H7	85	167	2.6
15	T15	4-CH3, 3,5-I	-C10H7	81	157	3.1
16	T16	5-Cl, 3-I	-C10H7	78	145	3.4

a- Yields were isolated and unoptimized b - ± 1oC

(T_1). White solid IR (KBr.) ν 3363, 3124, 2881, 2704, 1593, 1535, 1442, 1380, 1245, 1060, 999, 752 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.23 (CH benzene), 7.50 (CH benzene), 5.0 (OH), 6.6 (CH thaizole), 4.0 (NH_2), 2.23 (CH_3). Mass (m/z) M^+ 332, 260, 248, 120, 95, 67, 56

(T_2). White solid IR (KBr.) ν 3363, 3124, 2881, 2704, 1593, 1535, 1442, 1380, 1245, 1060, 999, 752 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.23 (CH benzene), 7.50 (CH benzene), 5.0 (OH), 6.6 (CH thaizole), 4.0 (NH_2), 2.23 (CH_3) Mass (m/z) M^+ 332, 260, 247, 118, 95, 67, 56

(T_3) White solid IR (KBr) **ν** 3340, 3120, 2790, 2690, 1590, 1520, 1440, 1310, 1240, 1070, 980, 750 $cm^{-1;}$ ^{1}HNMR ($CDCl_3$): δ 7.13 (CH benzene), 7.52 (CH benzene), 5.0 (OH), 6.64 (CH thaizole), 4.10 (NH_2), 2.24 (CH_3) Mass (m/z) 457, 385, 372, 122, 98, 69, 57.

(T_4) White solid IR (KBr.) ν 3320, 3118, 2782, 2695, 1585, 1515, 1435, 1320, 1245, 1070, 1060, 990, 750 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.22 (CH benzene), 7.50 (CH benzene), 5.1 (OH), 6.63 (CH thaizole), 4.05 (NH_2). Mass (m/z) 351, 280, 268, 108, 97, 68, 58.

(T_5) White solid IR (KBr.) ν 3315, 3197, 3110, 2909, 2882, 1519, 1477, 1321, 1064, 964, 755 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.3 (CH benzene), 7.27 (CH benzene), 5.2 (OH), 6.67 (CH thaizole), 5.15 (NH), 3.04 (NCH_3), 2.22 (CH_3) Mass (m/z) 346, 274, 245, 118, 97, 68, 56.

(T_6) White solid IR (KBr.) ν 3312, 3191, 3109, 2909, 2875, 1525, 1496, 1312, 1050, 967, 756 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.31 (CH benzene), 7.25 (CH benzene), 5.23 (OH), 6.66 (CH thaizole), 5.12 (NH), 3.0 (NCH_3), 2.21 (CH_3) Mass (m/z) 346, 274, 244, 119, 98, 68, 56.

(T_7) White solid IR (KBr.) ν 3310, 3197, 3100, 2900, 2880, 1515, 1476, 1322, 1050, 967, 756 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.32 (CH benzene), 7.27 (CH benzene), 5.2 (OH), 6.67 (CH thaizole), 5.16 (NH), 3.04 (NCH_3), 2.23 (CH_3) Mass (m/z) 472, 385, 373, 122, 97, 69, 57.

(T_8) White solid IR (KBr.) ν 3380, 3200, 3120, 2930, 2890, 1535, 1470, 1332, 967, 756 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.70 (CH thaizole), 5.25 (NH), 3.0 (NCH_3), Mass (m/z) 365, 279, 267, 108, 97, 69, 57.

(T_9) White solid IR (KBr.) ν 3340, 3187, 3109, 2500, 2890, 1525, 1486, 1332, 1060, 968, 759 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.3 (CH benzene), 7.27 (CH benzene), 5.2 (OH), 6.67 (CH thaizole), 5.15 (NH), 6.6-7.0 (CH Phenyl) 2.29 (CH_3) Mass (m/z) 408, 260, 245, 118, 97, 68, 56.

(T_{10}) White solid IR (KBr.) ν 3310, 3197, 3100, 2900, 2880, 1515, 1476, 1322, 1050, 967, 756 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.37 (CH thaizole), 5.25 (NH), 6.6-7.0 (CH Phenyl) 2.29 (CH_3) Mass (m/z) 408, 261, 243, 119, 98, 69, 56.

(T_{11}) White solid IR (KBr.) ν 3410, 3199, 3140, 2930, 2890, 1545, 1476, 1362, 1080, 987, 776 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.23 (CH benzene), 7.29 (CH benzene), 5.23 (OH), 6.77 (CH thaizole), 5.25 (NH), 6.6-7.0 (CH Phenyl) 2.19 (CH_3) Mass (m/z) 533, 385, 280, 120, 95, 67, 56.

(T_{12}) White solid IR (KBr.) ν 3310, 3197, 3100, 2900, 2880, 1515, 1476, 1322, 1050, 967, 756 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.67 (CH thaizole), 5.25 (NH), 6.6-7.0 (CH Phenyl) Mass (m/z) 428, 280, 268, 108, 97, 68, 57.

(T_{13}) White solid IR (KBr.) ν 3410, 3197, 3100, 2900, 2880, 1515, 1476, 1322, 1050, 967, 756 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.37 (CH thaizole), 5.25 (NH), 2.29 (CH_3) Mass (m/z) 458, 260, 248, 120, 95, 67, 56.

(T_{14}) White solid IR (KBr.) ν 3325, 3097, 2900, 2876, 1525, 1456, 1312, 1060, 964, 753 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.37 (CH thaizole), 5.25 (NH), 2.29 (CH_3) Mass (m/z) 458, 260, 248, 120, 95, 67, 56.

(T_{15}) White solid IR (KBr.) ν 3310, 3197, 3100, 2900, 2880, 1515, 1476, 1322, 1050, 967, 756 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.37 (CH thaizole), 5.25 (NH), 2.29 (CH_3) Mass (m/z) 584, 385, 372, 122, 98, 67, 56.

(T_{16}) White solid IR (KBr.) ν 3319, 3210, 3130, 2920, 2886, 1519, 1466, 1332, 1055, 965, 755 cm^{-1}**;** ^{1}HNMR ($CDCl_3$): δ 7.33 (CH benzene), 7.27 (CH benzene), 5.23 (OH), 6.37 (CH thaizole), 5.25 (NH), Mass (m/z) 478, 280, 268, 108, 97, 68, 57.

IV. CONCLUSION

In conclusion, we have described a simple, highly efficient, and facile protocol for the synthesis of 2-aminothiazole derivatives in water as reaction medium at ambient temperature. This process avoids the use of highly polar and toxic volatile organic solvents such as DMF, dioxane, and methanol, and catalyst, with the water itself playing the dual role of a solvent and promoter. Furthermore, the procedure offers several advantages including improved yields, simple experimental procedure, cleaner reactions, and low cost, which makes it a useful and attractive strategy in view of economic and environmental advantages. The successful application of this protocol for the preparation of the anti-inflammatory drug fanetizole is a significant contribution for the development of a green commercial process for the same.

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