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An Efficient and Rapid Synthesis of 2-Amino-4-Arylthiazoles Employing Microwave Irradiation in Water

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Abstract

A facile, high yielding green chemical synthetic protocol adaptable to the parallel synthesis of a library of potentially bioactive 2-amino-4-arylthiazoles is reported herein. The methodology involves the condensation of various aracyl bromides with N-arylthioureas under MWI using water as solvent, to yield pure products (81% - 97%) in very short reaction times (1-20 min).

Keywords: Green Chemical Synthesis, MWI, Water, 2-Amino-4-arylthiazoles

1. Introduction

Molecules containing a thiazole amine-moiety exhibit interesting biological activities depending on the substitution pattern at the thiazole ring [1]. 2-Aminothiazole nucleus is a potential pharmacophore for a broad spectrum of activities, comprising of antibacterial [2], antifungal [3], antitubercular [4], anti-HIV [5], pesticidal [6], anti-inflammatory [7], antiprotozoal [8] *etc*. Several methods reported for the synthesis of 2-aminothiazoles derivatives include Hantzsch reaction [9], solid supported [10] and solution phase [11] syntheses to generate libraries of these derivatives, as well as, those employing catalysts such as ammonium-molybdophosphate (AMP) [12], *β*-cyclodextrin [13], iodine [14], siliyl chloride [15], in organic as well as inorganic solvents at elevated temperatures [16,17]. However, these methods suffer from drawbacks like strong reaction conditions, low yields, cumbersome product isolation procedures as well as the use of expensive catalysts *etc*. The development of efficient and eco-friendly chemical processes for the preparation these thiazole derivatives is still a major need.

In recent times, water has shown great promise as an attractive alternative to conventional solvents (e.g., VOC's) [18]. It possesses the unique advantage of being costless and environmental friendly. Water not only acts as reaction media but also promotes the rate of reaction due to its ability to form hydrogen bonding as well as solvation effect.

Microwave Assisted Organic Synthesis (MAOS) has shown high impact in enhancing the rates of reaction and to speed up library syntheses for NDDR [19]. In recent years, synthesis of bioactive heterocycles using microwave irradiation has evolved as an important technique of green chemistry [20]. Water with the additive effect of microwave has been recognized as a green chemical component in the MAOS.

In continuation to our research work devoted to the development of green chemical techniques, we herein report an efficient method for the synthesis of 2-amino-4-arylthiazoles employing water as a solvent under MW irradiation. This novel process allows access to a library of 2-amino-4-arylthiazoles in very short reaction time without affecting the yield and purity of the target compounds.

2. Experimental

All reagents and chemicals used were of LR grade and purchased from standard vendors and used as received. Microwave synthesizer; (Questron Technologies Corporation, Canada; model-ProM) having monomode open-vessel was used for the synthesis. The ^{1}H NMR spectra were recorded in $CDCl_3$ using NMR Varian Mercury YH-300 MHz spectrometer and chemical shifts are given in units as per million, downfield from TMS (tetrame-

thylsilane) as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer. The Ultraviolet absorption spectra were determined in methanol on JASCO (Japan) V-530, UV-Visible double beam spectrophotometer. The IR spectra of the synthesized compounds were recorded on Perkin Elmer (USA) spectrum BX.FT-IR in potassium bromide discs.

2.1. Synthesis of Starting Materials

The substituted phenacyl bromides **(1-4)** [21] and substituted N-phenylthioureas **(5-14)** [22] were prepared by reported procedures.

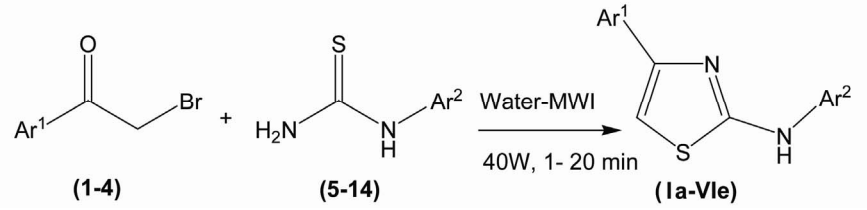
2.2. Synthesis of 2-phenylamino-4-phenylthiazole (I*a*-IV*e*) by Using Water as Solvent under Microwave Irradiation (General Procedure)

In a 20 ml reaction vessel containing phenacyl bromide (1 gm, 0.0036 mol) and N-phenyl thiourea (0.29 gm, 0.003 mol) was added water (5 ml). Thereafter, the reaction mixture was irradiated under microwave (40 W) for appropriate time **(Table 1**). The completion of reaction was monitored by TLC, the solid separated was filtered, washed with water and recrystallised.

3. Results and Discussion

Literature survey revealed that most of the reported conventional routes, afford 2-amino-4-arylthiazoles in 72% - 80% yields in an overall reaction time of 6 - 18 hr. We aimed at preparing these compounds employing green chemical synthetic procedures which could be adaptable to parallel syntheses for making compounds libraries. An efficient method using water as solvent for the synthesis of 2-amino-4-arylthiazoles under MWI is reported herein. Phenacyl bromides carrying different functional groups such as EDG and EWG were subjected to study their reaction with various N-aryl thioureas. The results are presented in **Table 1**. The reaction protocol affords good overall yields (81% - 97%) and in very short reaction time (01-20 min) (**Scheme 1**).

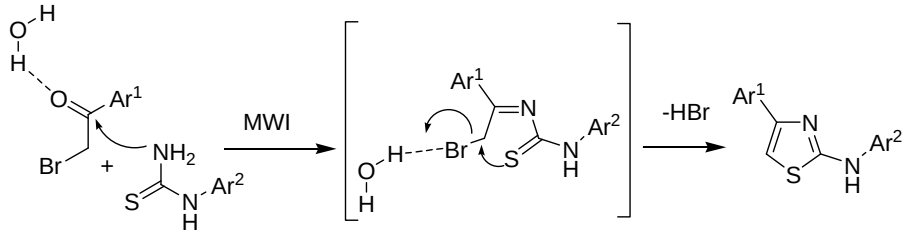
Water when used as a solvent under MWI promotes the



Scheme 1. Synthesis of 2-amino-4-aryl-thiazoles.

reaction through hydrogen bond formation with carbonyl oxygen of the phenacyl bromide in presence of microwave energy. This leads in the enhancement of electrophilicity of the carbonyl carbon and facilitates the nucleophilic attack by the amino nitrogen of the thioamide. This is further followed by the intramolecular nucleophilic attack by the sulphur on the bromomethyl carbon, leading to the formation of thiazole through the removal of an HBr molecule (**Scheme 2**).

Thus, we have been successful in developing a rapid



Scheme 2. Proposed mechanism for the synthesis of thiazole.

green chemical synthetic procedure which can be made adaptable to high throughput parallel synthesis of compound libraries of 2-amino-4-arylthiazoles with an added advantage of considerable improvement in the yields of the target compounds without affecting their purity.

4. Conclusions

We have developed a mild, convenient, ecofriendly and efficient protocol for the rapid synthesis of 2-substitutedarylamino-4-substitutedarylthiazoles. The process offers excellent yields of 2-substitutedarylamino-4-sub-

Table 1. Physical data for the 2-arylamino-4-arylthiazoles (I*a*-IV*e*).

Com. No.	Ar^1	Ar^2NH	By MWI-H_2O		
			Time (min)	M. P. (˚C)	Yield (%)
I*a*	C_6H_5	C_6H_5	10	134-135	88
I*b*	C_6H_5	4-ClC_6H_4	15	148-150	90
I*c*	C_6H_5	4-$CH_3C_6H_4$	15	115-116	87
I*d*	C_6H_5	4-$NO_2C_6H_4$	15	202-203	91
I*e*	C_6H_5	4-FC_6H_4	15	90-91	89
I*f*	C_6H_5	2-ClC_6H_4	10	75-77	96
I*g*	C_6H_5	3-ClC_6H_4	2	85-87	88
I*h*	C_6H_5	2-$CH_3C_6H_4$	2	104-106	85
I*i*	C_6H_5	3-$CH_3C_6H_4$	2	137-140	85
I*j*	C_6H_5	4$CH_3OC_6H_4$	1	147-159	95
II*a*	4-ClC_6H_4	C_6H_5	15	137-138	86
II*b*	4-ClC_6H_4	4-ClC_6H_4	10	231-232	87
II*c*	4-ClC_6H_4	4-$CH_3C_6H_4$	15	168-170	86
II*d*	4-ClC_6H_4	4- $NO_2C_6H_4$	15	253-255	85
II*e*	4-ClC_6H_4	4-FC_6H_4	20	169-170	82
II*f*	4-ClC_6H_4	2-ClC_6H_4	20	132-134	83
II*g*	4-ClC_6H_4	3-ClC_6H_4	1	144-146	98
II*h*	4-ClC_6H_4	2-$CH_3C_6H_4$	5	108-110	93
II*i*	4-ClC_6H_4	3-$CH_3C_6H_4$	1	190-192	97
II*j*	4-ClC_6H_4	4$CH_3OC_6H_4$	1	160-162	94
III*a*	4-BrC_6H_4	C_6H_5	15	103-104	88
III*b*	4-BrC_6H_4	4-ClC_6H_4	15	140-142	84
III*c*	4-BrC_6H_4	4-$CH_3C_6H_4$	20	129-130	87
III*d*	4-BrC_6H_4	4-NO_2 C_6H_4	15	244-246	81
III*e*	4-BrC_6H_4	4-FC_6H_4	15	107-108	82
IV*a*	4-$CH_3C_6H_4$	C_6H_5	20	92-93	89
IV*b*	4-$CH_3C_6H_4$	4-ClC_6H_4	20	71-72	84
IV*c*	4-$CH_3C_6H_4$	4-CH_3C_6H4	20	44-45	87
IV*d*	4-$CH_3C_6H_4$	4- $NO_2C_6H_4$	20	73-75	90
IV*e*	4-$CH_3C_6H_4$	4-FC_6H_4	20	103	88

Representative Data of Target Compounds:

2-(2-*Chlorophenyl*)*amino*-4-*phenylthiazole* ***If***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.92(1H, s, NH D_2O exchangeable); 7.27 - 8.29(10H, m, Ar-*H* and thiazole proton at 5). IR (KBr) cm^{-1}: $3206_{[\gamma NH]}$, $3065_{[\gamma C\text{-}H]}$. *m/z* 286($M^+$). Anal. Calcd. for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; N, 9.77; found C, 62.76; H, 3.71; N, 9.93;

2-(4-*Chlorophenyl)amino*-4-(4-*chlorophenyl)thiazole* **II*b***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.77(1H, s, NH D_2O exchangeable); 6.99-7.98(9H, m, Ar-*H* and thiazole proton at 5). IR (KBr) cm^{-1}: $3335_{[\gamma NH]}$, $2922_{[\gamma C\text{-}H]}$. *m/z* 323 (M+2). Anal. Calcd. For $C_{15}H_{10}Cl_2N_2S$: C, 56.09; H, 3.14; N, 8.72; found C, 55.82; H, 3.11; N, 8.86;

2-(4-*Fluorophenyl)amino*-4-(4-*chlorophenyl)thiazole* **II*e***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.71(1H, s, NH D_2O exchangeable); 7.08-7.99 (9H, m, Ar-*H* and thiazole proton at 5). IR (KBr) cm^{-1}: $3251_{[\gamma NH]}$, $3065_{[\gamma C\text{-}H]}$. *m/z* 304 ($M^+$). Anal. Calcd. for $C_{15}H_{10}ClFN_2S$: C, 56.11; H, 3.31; N, 9.19; found C, 56.05; H, 3.24; N, 9.11;

2-(4-*Methoxylphenyl)amino*-4-(4-*chlorophenyl*)*thiazole* **II*j***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.85(3*H*, s, CH_3), 6.64(1H, s, NH D_2O exchangeable); 6.95 - 7.75 (9H, m, Ar-*H* and thiazole proton at 5). IR (KBr) cm^{-1}: $3401_{[\gamma NH]}$ $3164_{[\gamma C\text{-}H]}$. *m/z* 316($M^+$). Anal. Calcd. for $C_{16}H_{13}ClN_2OS$: C, 60.66; H, 4.14; N, 8.84; found C, 60.36; H, 4.03; N, 8.67;

2-(4-*Chlorophenyl)amino*-4-(4-*bromophenyl)thiazole* **III*b***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.64(1H, s, NH D_2O exchangeable); 7.25-7.71(9H, m, Ar-H and thiazole proton at 5). IR (KBr) cm^{-1}: $3367_{[\gamma NH]}$, $2935_{[\gamma C\text{-}H]}$. *m/z* 366 ($M^+$). Anal. Calcd. for $C_{15}H_{10}BrClN_2S$: C, 49.27; H, 2.76; Br, 21.85; N, 7.66; found C, 49.01; H, 2.48; N, 7.54;

2-(4-*Methylphenyl)amino*-4-(4-*methylphenyl*)*thiazole* **IV*c***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.38(6H, s, C*H*$_3$); 6.57(1H, s, NH); 7.2-7.7(9H, m, Ar-H and *H*- of thiazole). IR (KBr) cm^{-1}: $3437_{[\gamma NH]}$, $2923_{[\gamma C\text{-}H]}$. *m/z* 280($M^+$). Anal. Calcd. for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99 ; found C, 72.76; H, 5.59; N, 9.84;

2-(4-*Fluorophenyl)amino*-4-(4-*methylphenyl*)*thiazole* **IV*e***: ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.40 (3H, d, C*H*$_3$); 6.69(1H, s, NH); 6.9 - 8.0 (8H, m, Ar-H); 7.99 (1H, s, thiazole *H*). IR (KBr) cm^{-1}: $3144_{[\gamma NH]}$, $2923_{[\gamma C\text{-}H]}$. *m/z* 284($M^+$). Anal. Calcd. for $C_{16}H_{13}FN_2S$: C, 67.58; H, 4.61; N, 9.85; found C, 67.48; H, 4.56; N, 9.69;

stitutedarylthiazoles under green chemical conditions in very short reaction times.

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