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AQUA MEDIATED NOVEL, ONE-POT, CATALYST-FREE AND ECONOMICALLY EFFICIENT SYNTHESIS OF FUNCTIONALIZED 2-AMINOTHIAZOLES

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ABSTRACT

A fast, economically and environment-friendly one-pot method has been developed for the synthesis of 2-aminothiazoles in water without using any catalyst or hazardous co-organic solvent. The products were produced in excellent isolated yields and crude products do not require any further purification. This simple methodology gave an access to a wide range of 2-aminothiazoles and can be employed for the synthesis of many pharmaceutical precursors.

KEYWORDS: 2-Aminothiazoles, Environmental Benign Synthesis, Water

INTRODUCTION

In these days, the environmental protection become a global concern and therefore it is one of the most challenging fields for the chemists to search the ways of developing and applying more efficient environmentally benign strategies for sustainable future growth. One of the trust areas for achieving this target is use of green chemistry techniques.

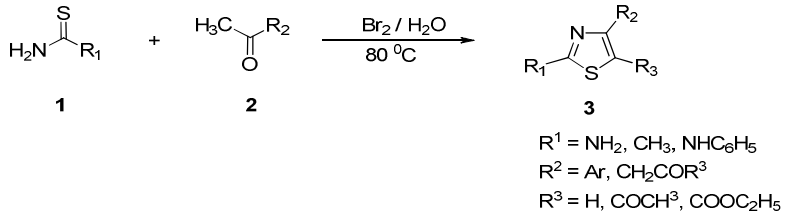
Thiazoles display a broad range of biological activities and found to be present in many pharmaceutically important molecules such as sulfathiazole (antimicrobial), triazofurin (antineoplastic), ritonavir (antiretroviral), abafungin (antifungal) etc. Thiazole ring possessed the important constituent of many natural products such as Vitamin B1[1], Bacillamide[2] and Epothilones[3]. Its derivatives particularly 2-aminothiazole have shown a wide variety of biological activities like antimicrobial[4,5] antitumor,[6] anti-inflammatory,[7,8] antifungal,[9,10] antitubercular,[11,12] anticonvulsant[13] and antiallergic[14]. Further, aminothiazoles can also be used as neuroprotective,[15] antioxidant activity[16] and acetyl-Co-A carboxylase inhibitors[17]. So, the development of library of 2-aminothiazoles might furnish the additional lead molecules for the drug discovery. In last ten years there were more than 2500 publications on thiazoles, which itself indicates the importance of this molecule. Therefore in view of high importance of 2-aminothiazoles in medicinal chemistry several attempts were made for developing synthetic methodologies to synthesize them.

The most commonly used method is Hantzsch synthesis[18] involving the reaction of α-halocarbonyl compounds with thioureas or thioamides. Thiazole moiety were also obtained by using a two-stage scheme, which includes bromination of the initial ketones in diethyl ether in the presence of $AlCl_3$[19] or in methanol-acetone mixture[20] followed by cyclocondensation of the bromoketones intermediate with thiourea in ethanol. However these protocols were suffered from many serious drawbacks, such as the formation of intermediate α-bromoketones which possess lachrymatory properties and hence was difficult to handle, low yields, harsh reaction conditions, long reaction times and the use of volatile organic solvent. Therefore improvement in the synthetic methodologies have been made which includes the use of catalyst such as

ammonium-12-molybdophosphate in methanol,[21] β-cyclodextrin in water,[22] iodine[23] and by using microwave in I_2/ethanol.[24] Inspite of potential utility of some of these methods, they suffer from drawbacks, such as harsh reaction conditions, prolonged reaction time, unsatisfactory yield, usage of hazardous organic solvents and expensive catalysts. Thus the development of a simple and efficient method under greener reaction conditions for selective construction of thiazole derivatives have been advocated. The tight legislation to maintain greenness requires us to prevent the generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagents) and minimize the energy requirement. In this context, the use of water as the reaction medium in the organic chemistry was first rediscovered in the 1980s by Breslow.[25] In this paper we are concerning the use of water as an eco-compatible reaction solvent and keeping in mind that 'the best catalyst is no catalyst," we report novel and economically effective method for the synthesis of 2-aminothiazole obtained "in one pot," by initially conducting monobromination of ethylacetoacetate / acetylacetone/ substituted acetophenones in situ followed by cyclocondensation of the intermediate with thiuourea or thioamides.

RESULTS AND DISCUSSIONS

When bromine was added to a mixture of ethylacetoacetate (**1a**) and thiourea (**2a**) in water as solvent and heated at 80 °C, resulted in the formation of **3a** surprisingly in a higher 89% yield just in 8 hours (Scheme 1). The formation of compound **3a** was confirmed as 2-amino-5-carboethoxy-4-methylthiazole on the basis of its detailed spectral analysis such as IR, ^{1}H NMR and mass spectroscopy.



Scheme 1: Synthesis of 2-Aminothiazole in Water

To find out if water provides a kinetic advantage over the use of various solvents such as dichloromethane, tetrahydrofuran, acetonitrile, ethanol, dimethyl sulfoxide and distilled water under identical conditions, we reacted ethylacetoacetate (**1a**) and thiourea (**2a**) in presence of bromine and **3a** was formed in different yields as shown in Table 1. The results of our experiments indicates that the reactions in ethanol and acetonitrile also delivered the desired compound in good yields but a maximum yield of 89 % could only be obtained using water as solvent.

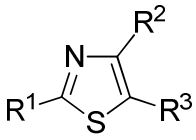
Table 1: Synthesis of 2-Aminothiazole Using Different Organic Solvents

Entry	Solvent	Conditions [a]	Yield [b] (%)
1	CH_2Cl_2	reflux	14%
2	THF	reflux	12%
3	CH_3CN	reflux	68%
4	C_2H_5OH	reflux	70%
5	DMSO	100°C	32%
6	distilled H_2O	80°C	82%
7	Tape H_2O	80°C	89%

[a] reaction time 8 hours,
[b] all yield reflect to isolated product.

Similar reaction was also carried out in distilled water, no significant difference was observed in reaction with distilled water and tap water either in terms of reaction time or in the product yields. Thus the reactions were simply carried out in the tap water so that the extra efforts and the energy required to prepare distilled water can be ignored. The products were obtained in highly pure form and do not require any further purification by column chromatography or by any other methods, the yields were significantly higher as compared to those obtained for the volatile/ toxic/polar organic solvents. After optimizing the conditions, we next examined the scope and generality of this greener method to other substrates using different substituted ketones and thioureas and the result are summarized in Table 2.

Table 2: Synthesis of 2-Aminothiazoles in Water



Entry	R^1	R^2	R^3	Product 3	Time (h)	Yield[a] (%)	Mp[b] (°C)	Lit. mp[c] (°C)
1	NH_2	CH_3	$COOC_2H_5$	**3a**	2.5	89	103	106[26]
2	CH_3	CH_3	$COOC_2H_5$	**3b**	3.0	85	194	195[26]
3	NHC_6H_5	CH_3	$COOC_2H_5$	**3c**	3.5	82	140	142[27]
4	NH_2	CH_3	$COCH_3$	**3d**	2.0	87	258	260[28]
5	CH_3	CH_3	$COCH_3$	**3e**	2.5	84	232	230[29]
6	NHC_6H_5	CH_3	$COCH_3$	**3f**	2.0	88	160	152[30]
7	NH_2	p-CH_3-C_6H_4	H	**3g**	4.5	82	138	137[31]
8	CH_3	p-CH_3-C_6H_4	H	**3h**	3.5	81	65	64[32]
9	NHC_6H_5	p-CH_3- C_6H_4	H	**3i**	2.0	83	170	171[31]
10	NH_2	p-Cl- C_6H_4	H	**3j**	2.0	85	175	176[31]
11	CH_3	p-Cl- C_6H_4	H	**3k**	3.0	87	120	122[33]
12	NHC_6H_5	p-Cl- C_6H_4	H	**3l**	2.0	82	154	153[31]
13	NH_2	p-Br- C_6H_4	H	**3m**	2.0	80	181	182[31]
14	CH_3	p-Br- C_6H_4	H	**3n**	3.0	82	163	165[31]
15	NHC_6H_5	p-Br- C_6H_4	H	**3o**	2.0	87	143	144[31]

[a] all yield reflect to isolated product,
[b] observed melting point,
[c] literature melting point.

The synthesized 2-aminothiazole derivatives were identified and confirmed by elemental analyses and from spectral studies and also by comparison of their melting points values with those previously described in literature.[26-33]

EXPERIMENTAL

Melting points were determined on an electronic apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) were recorded on Bruker Advance (100 MHz) using tramethylsilane (TMS) as an internal standard and $CDCl_3$/$DMSOd_6$ as solvent. TOF ES+ Mass spectra (m/z) were recorded on Micromass Autospec LCTKC455. Infrared (FTIR) spectra were determined on a Perkin Elmer-2000 Spectrophotometer instrument. The chemicals used in this work were purchased from Mreck and were used without further purification.

General Procedure for the Synthesis of 2-Aminothiazoles

To the mixture of ethylacetoacetate or acetylacetone or *p*-subtituted acetophenone (1.0 mmol) and substituted thiourea or thioamide (1.5 mmol), in 15 mL of water, bromine (1.5 mmol) were added drop-wise in the period 10 minutes. After the complete addition of bromine, reaction mixture was heated on an oil-bath at 70-80 °C for 7-8 hours.

Then contents were filtered while hot. The filtrate was cooled and aqueous solution of K_2CO_3 was added. A white solid that separated out was filtered and dried under reduced pressure to obtain the desired 2-aminothiazoles.

2-Amino-5-Carboethoxy-4-Methylthiazole (3a): White solid; R_f = 0.44 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3374, 3300, 2978, 1721, 1675, 1654, 1516, 1370, 1278, 1096, 758; ^1H NMR (δ, $CDCl_3$, 400 MHz): 5.59 (brs, 2H, NH_2, D_2O exchangeable), 4.27 (q, 2H, OCH_2), 2.56 (s, 3H, 4-CH_3), 1.31 (t, 3H, CH_3); Mass spectral data, TOF ES+ *m/z* (%): 187 (M^++1).

5-Carboethoxy-2, 4-Dimethyl Thiazole (3b): White solid; R_f = 0.42 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3231, 2954, 1720, 1642, 1520, 1431, 1208, 1101, 740; ^1H NMR ($CDCl_3$, 400 MHz, *δ*, ppm): 4.14 (q, 2H, OCH_2), 2.76 (s, 3H, 2-CH_3), 2.24 (s, 3H, 4-CH_3), 1.18 (t, 3H, CH_3); Mass spectral data, TOF ES+ m/z (%): 186 (M^++1).

5-Carboethoxy-4-Methyl-2-(*N*-Phenyl) Aminothiazole (3c): White solid; R_f = 0.45 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3374, 3082, 2978, 1722, 1516, 1370, 1278, 1096, 758; ^1H NMR ($CDCl_3$, 400 MHz, *δ*, ppm): 10.40 (s, 1H, NH, D_2O exchangeable proton), 7.38 (m, 1H), 7.32(m, 2H), 7.29 (d, 2H, *J*= 7.8 Hz), 4.25 (q, 2H, OCH_2), 2.51 (s, 3H, 4-CH_3), 1.32(t, 3H); Mass spectral data, TOF ES+ m/z (%): 263 (M^++1).

5-Acetyl-2-Amino-4-Methylthiazole (3d): White solid; R_f = 0.46 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3372, 3300, 2969, 1710, 1650, 1516, 1279, 1095, 757; ^1H NMR ($CDCl_3$, 400 MHz, δ, ppm): 5.71 (brs, 2H, D_2O exchangeable, NH_2), 2.43 (s, 3H, 4-CH_3), 2.21 (s, 3H, $COCH_3$); Mass spectral data, TOF ES+ *m/z* (%): 157 (M^++1).

5-Acetyl -2,4-Dimethylthiazole (3e): White solid; R_f = 0.45 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3369, 3282, 2956, 1715, 1652, 1524, 1223, 1121, 782; ^1H NMR ($CDCl_3$, 400 MHz, *δ*, ppm): 2.89 (s, 3H, 2-CH_3), 2.27 (s, 3H, 4-CH_3), 2.20 (s, 3H, $COCH_3$); Mass spectral data, TOF ES+ *m/z* (%): 156 (M^++1).

5-Acetyl-4-Methyl-2-(N-Phenyl) Aminothiazole (3f): White solid; R_f = 0.45 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, $cm.^{-1}$): 3372, 3300, 2969, 1712, 1650, 1516, 1279, 1095, 757; ^1H NMR ($CDCl_3$, 400 MHz, *δ*, ppm): 10.30 (s, 1H, NH, D_2O exchangeable proton), 7.23 (m, 2H), 7.19 (m, 1H), 7.13 (d, 2H, *J*= 7.5 Hz), 2.43 (s, 3H, thiazole CH_3), 2.21 (s, 3H, $COCH_3$); Mass spectral data, TOF ES+ m/z (%): 232 (M^++1).

2-Amino-4-(4-Methylphenyl) Thiazole (3g): White solid; R_f = 0.43 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3412, 3264, 1632, 1470, 1362, 1118, 764, 682; ^1H NMR (δ,$CDCl_3$, 400 MHz): 7.30 (d, 2H, *J* = 7.9 Hz), 7.16 (d, 2H, *J*= 7.9 Hz), 6.35(s, 1H), 4.98 (brs, 2H, NH_2, D_2O exchangeable), 2.34(s, 3H, CH_3). Mass Spectral data, TOF ES+ m/z (%): 191 (M^++1).

2-Methyl-4-(4-Methylphenyl)T hiazole (3h): White solid;; R_f = 0.46 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3289, 1643, 1492, 1295, 1208, 1107, 798; ^1H NMR (δ, $CDCl_3$, 400 MHz): 7.30 (d, 2H, *J*= 7.9 Hz), 7.16 (d, 2H, *J*= 7.9 Hz), 6.68(s, 1H), 2.81(s, 3H, 2-CH_3), 2.28(s, 3H, CH_3); Mass Spectral data, TOF ES+ m/z (%): 190 (M^++1, 100).

4-(4-Methylphenyl)-2-(*N*-Phenyl) Aminothiazole (3i): White solid; R_f = 0.44 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3383, 2925, 1616, 1567, 1477, 1401, 1302, 1091, 829; ^1H NMR

(δ, $CDCl_3$, 400 MHz): 9.22(s, 1H, NH, D_2O exchangeable proton), 7.70 (d, 2H, *J*= 8.2 Hz), 7.38 (m, 4H), 7.19(m, 3H), 6.66(m, 1H), 2.36(s, 3H, CH_3); Mass Spectral data, TOF ES+ m/z (%): 267(M^++1).

2-Amino-4-(4-Chlorophenyl)Thiazole (3j): White solid; R_f = 0.43 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3381, 3264, 1620, 1543, 1495, 1392, 743, 652; ^{1}H NMR (δ, $CDCl_3$, 400 MHz): 7.51 (d, 2H, *J*= 8.1Hz), 7.18 (d, 2H, *J*= 8.1 Hz), 6.67 (s, 1H), 4.91 (brs, 2H, NH_2, D_2O exchangeable); Mass spectral data, TOF ES+ m/z (%): 211 (M^++1).

4-(4-Chlorophenyl)-2-Methylthiazole (3k): White solid; R_f = 0.44 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): ν_{max} (KBr): 3071, 2894, 1622, 1582, 1432, 1332, 1294, 1103, 743, 652; ^{1}H NMR (δ, $CDCL_3$-d_6, 400 MHz): 7.30 (d, 2H, *J*= 7.9 Hz), 7.16 (d, 2H, *J*= 7.9 Hz), 6.68(s, 1H), 2.81(s, 3H, 2-CH_3); Mass spectral data, TOF ES+ m/z (%): 210 (M^++1).

4-(4-Chlorophenyl)-2-*N*-Phenylaminothiazole (3l): White solid; R_f = 0.46 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3380, 2981, 1645, 1462, 1378, 1254, 1118, 775, 613; ^{1}H NMR (δ, $CDCl_3$, 400 MHz): 10.71 (s, 1H, NH, D_2O exchangeable proton), 7.51 (d, 2H, *J*= 8.2 Hz), 7.34 (m, 1H), 7.21 (d, 2H, *J*= 8.2 Hz), 6.62 (d, 2H, *J*= 8.0 Hz), 6.41 (m, 2H), 6.70 (s, 1H); Mass spectral data, TOF ES+ m/z (%): 287 (M^++1).

2-Amino-4-(4-Bromophenyl) Thiazole (3m): White solid; R_f = 0.46 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3370, 3271, 2987, 1629, 1460, 1371, 768, 670; ^{1}H NMR (δ,$CDCl_3$, 400 MHz): 7.49 (d, 2H, *J*= 7.6 Hz), 7.46 (d, 2H, *J*= 7.6 Hz), 6.59 (s, 1H), 4.89 (brs, 2H, NH_2, D_2O exchangeable); Mass spectral data, TOF ES+ m/z (%): 255 (M^++1).

4-(4-Bromophenyl)-2-Methylthiazole (3n): White solid; R_f = 0.42 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3439, 3113, 1626, 2920, 1505, 1321, 1187, 743; ^{1}H NMR (δ,$CDCl_3$, 400 MHz): 7.74 (d, 2H, J=8.1), 7.52 (d, 2H, J=8.1), 7.30(s, 1H), 2.76(s, 3H, CH_3); Mass spectral data, TOF ES+ m/z (%): 254 (M^++1).

4-(4-Bromophenyl)-2-(*N*-Phenyl) Thiazole (3o): White solid; R_f = 0.44 in chloroform/methanol (98:2) as developing solvent system. IR (KBr, cm^{-1}): 3330, 3121, 2923, 1627, 1581, 1402, 1387, 1129, 823; ^{1}H NMR (δ,$CDCl_3$, 400 MHz): 10.5 (s, 1H, NH, D_2O exchangeable proton), 7.71 (d, 2H, *J*= 8.1 Hz), 7.51 (d, 2H, *J*= 8.0 Hz), 7.39 (m, 4H), 7.08 (m, 1H), 6.81 (s, 1H); Mass spectral data, TOF ES+ m/z (%): 331 (M^++1).

CONCLUSIONS

In conclusion, we have developed a new, economically efficient and greener one-pot method for the synthesis of 2-aminothiazole derivatives in water at moderate temperature. The important features of this methodology are improved higher yields, only in a single step, enhanced reaction rate, mild reaction conditions, and greener aspects, such as avoiding hazardous organic solvents, toxic and expensive catalysts, easy experimental procedure and water used as medium in the reaction and as well as promoter.

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