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NOVEL MULTICOMPONENT APPROACH FOR SYNTHESIS OF 2-AMINO THIAZOLE AT ROOM TEMPERATURE

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Abstract
A multicomponent, room temperature reaction between substituted isothiocyantes, amines and α-bromocarbonyl compound was carried out in dimethyl sulfoxide in the presence of the Triton-B to synthesize a library of 2-amino thizole. This process was found to be suitable for the synthesis of variety of 2-amino thiazoles using aliphatic and aromatic amines.
Keywords: Multicomponent, Isothiocyanates, α-Bromocarbonyl, Triton-B, 2-Aminothiazole

Introduction:

2-amino thiazole have been found to a prominent core for the drug development as it has been found to possess library of the biological activities like antimicrobial [1], anti-HIV, antioxidant, anticancer [2,3, 4], antitubercular [5], anti-inflammatory [6],antiprion [7], antiviral [8]. The potential activities of the 2-aminothiazole motivated the medicinal scientist globally and many synthetic procedures have been reported till now [2,9]. The Hantzsch condensation employing α-halocarbonyls and thioureas has been a prominent method for their synthesis.

Many synthetic methods [11-17] have been reported for the improvement of the Hantzsch synthesis [10]. Though these methods have been a improvement in the process yet they are still not free from using toxic reagents, hectic work-up and the reaction conditions are also very harsh [11-17].

So the development of the cleaner, greener, economical process with easier workup and higher yield is desirable and welcoming. In this development we would like to make a potential improvement in the process for the synthesis of the 2-aminothiazoles through We are involved in the synthesis of biologically potent scaffolds involving cleaner and greener methods since past 10 years [18]. In the present communication we are reporting the cleaner, greener, easier, and efficient method for the synthesis of 2-aminothiazoles.

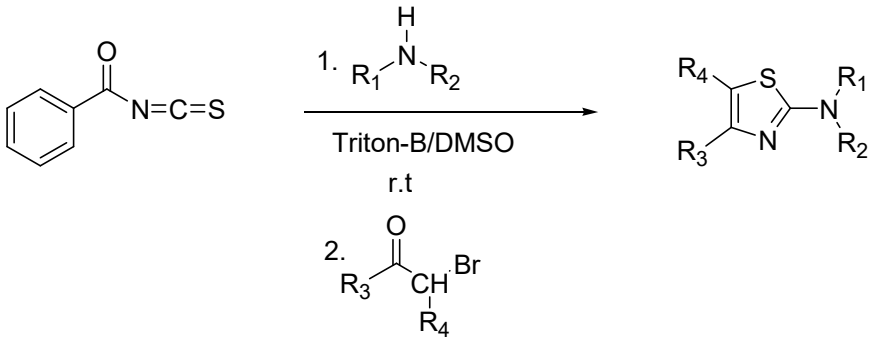
Experimental:

Material and Methods: All the reagents used were purchased from Fluka, Aldrich and Merck. Inert atmosphere of nitrogen deployed in carrying out the reaction process. IR spectra of the synthesized compounds were done on Bomem MB-104–FTIR spectrophotometer while ^{1}H NMR spectra were

recorded on AC-300F, NMR (300 MHz), with $CDCl_3$ as solvent and in reference to tetramethyl silane (TMS). Carlo-Erba EA 1110-CNNO-S analyzer was used for analysis of the elements in the compound

General procedure:

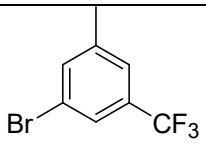
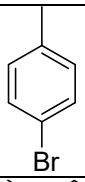
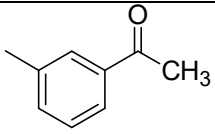
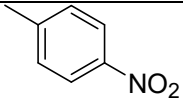
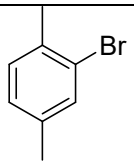
1 mmol of benzoyl isothiocyanate (**1**) was taken in round bottom flask and added slowly with 1.5 mmol of aliphatic or aromatic amine (**2**) and mixed with 1 mol of Triton-B and then with α-bromocarbonyl compound (**3**). Now the components of the reaction mixture were stirred at room temperature for 30 min. The organic layer was filtered and dried in the presence of anhydrous Na_2SO_4 and compound was extracted in the presence of ethyl acetate. It was further concentrated on rotatory evaporator and chiller. The purification of the product was done by column chromatography using 1:10 ethyl acetate and n-hexane for elution.

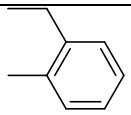
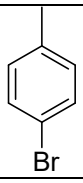
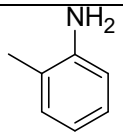
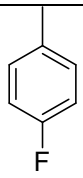
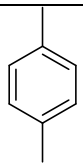
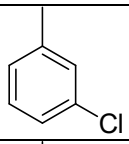
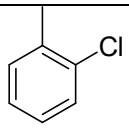
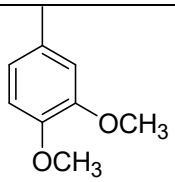
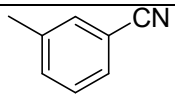


Scheme 1 Synthesis of 2-aminothiazole

Various 2-aminothiazoles were synthesized using variety of aromatic and aliphatic amines and the α-bromocarbonyl compound using Triton-B as phase transfer catalyst as summarized in table 1

Table 1- Various synthesized 2-aminothiazoles

Entry	**R_1**	**R_2**	**R_3**	**R_4**	**Time (min)**	**Yield**
1	4-Br-C_6H_4	H	H	-C_6H_5	5	96
2		H	H		5	85
3		H	H		5	75
4		H	-C_6H_5	-CH_3	5	96

5		-	H	$-C_6H_5$	5	96
6		-	H		5	90
7	$-C_4H_9$	H	H	Ph	5	75
8		H	H	Ph	5	78
9		H	H	$-COOC_2H_5$	10	90
10		H	H	$-COOC_2H_5$	10	92
11		H	H	$-COOC_2H_5$	10	70
12		H	H	$-COOC_2H_5$	10	75
13		H	$-C_6H_5$	$-CH_3$	10	96
14		H	$-C_6H_5$	$-CH_3$	10	78

The synthesized compounds were purified by adding water to Compound. Compounds in the pure form were obtained as insoluble salts after filtration with the yield of (70–98%). The extra reagents were recovered by evaporation. In summery a cleaner, greener, efficient protocol has been developed for the synthesis of 2-aminothiazoles using cheaper and easily available reagents.

Data of the Synthesized compounds:

1. (4-Bromo-phenyl)-(4-phenyl-thiazol-2-yl)-amine

Beige solid; yield: 171 mg (94%); mp 229–231 °C; ^{1}H NMR (400 MHz, acetone-*d*6): δ 7.80–7.76 (m, 2 H, Ph), 6.93–6.89 (m, 2 H, Ph), 6.76 (s, 1 H, H5), 6.35 (br s, 2 H, NH2), 3.80 (s, 3 H, OCH3). ^{13}C NMR (100 MHz, acetone-*d*6): δ 169.7 (C2), 160.9 (C4′), 152.5 (C4), 130.1 (Ph), 128.8 (Ph), 115.4 (C3′), 101.2 (C5), 56.4 (OCH3); MS (ESI): *m*/*z* = 206.9 ([M]$^{+}$, 100%).

2. ***[4-(4-Bromo-phenyl)-thiazol-2-yl]-(3-bromo-5-trifluoromethyl-phenyl)-amine***

White solid, mp = 230-234 °C;^{1}H NMR (400 MHz, DMSO-*d*6) : δ 9.61 (br s, 2H), 7.49 (t, *J* = 1.5 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 7.5 Hz, 1H), 6.98 (m, 1H), 6.59 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 7.44 (s, 1H); ^{13}C N MR (100 MHz, DMSO-*d*6) : δ 173.3, 150.8, 149.1, 147.0, 135.5, 134.0,132.3, 129.1, 124.12, 123.1, 121.7, 118.6, 110.9, 103.4; Anal. Calcd for $C_{16}H_9Br_2F_3N_2S$: C, 40.19; H, 1.90; Br, 33.42; F, 11.92; N, 5.86; S, 6.71. Found: C, 40.20; H, 1.89; Br, 33.48; F, 5.87; S, 6.85. m/e=477.8785

3. ***1-{3-[4-(4-Nitro-phenyl)-thiazol-2-ylamino]-phenyl}-ethanone***

beige solid, mp = 247-249 °C;^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.61 (br s, 2H), 8.28 (t, *J* = 1.5 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.74 (m, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.44 (s, 1H), 2.58 (s, 3H);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 196.3, 169.2, 147.1, 138.0, 137.6, 134.2, 133.1, 132.4, 130.3, 130.2, 129.7, 128.2, 122.9, 107.5, 26.3; Anal. Calcd for C17H14BrN3O3S: C, 48.58; H, 3.36; N, 10.00. Found: C, 48.68; H, 3.42; N, 9.89

4. ***Butyl-(4-phenyl-thiazol-2-yl)-amine***

white solid, mp = 120-125 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.22 (s, 1H), 6.76 (s, 1 H, H5), 6.35 (br s, 1H, NH), 4.68 (s, H), 3.06 (t, *J* = 5.5 Hz, 2H), 1.52 (m, *J* = 5.5 Hz, 2H), 1.33 (m, *J* = 5.5 Hz, 2H), 0.96(t, *J* = 5.5 Hz, 2H) ;^{13}C NMR (125 MHz, DMSO-*d*6) : δ 173.2, 150.8, 136.5, 129.7, 129.0, 128.5, 127.0, 103.4, 51.0, 34.0, 20.7, 13.7 Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 67.12; H, 6.96; N, 12.10; S, 13.82. m/e= 232.1034

5. ***N-(4-Phenyl-thiazol-2-yl)-benzene-1,2-diamine***

white solid, mp = 123-125 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.22 (s, 1H), 6.76 (s, 1 H), 6.76 (br, s, 2H, NH_2), 6.35 (br s, 1H, NH), 6.37-6.21 (m 4H aromatic);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 173.2, 150.8, 136.5, 129.7, 129.0, 147.2, 128.5, 127.0, 124.3, 118.4. Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72; S, 11.99. Found: C, 67.13; H, 4.93; N, 15.70; S, 12.02. m/e= 267.0830

6. ***2-(4-Fluoro-phenylamino)-thiazole-4-carboxylic acid ethyl ester***

white solid, mp = 141-145 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.34 (1H), 4.29 (d, *J* = 8.5 Hz, 2H), 1.30 (t, *J* = 6.5 Hz, 3H), 6.72-6.44 (m, 4H), 6.76 (s, 1 H), 6.89 (br, s, 2H, NH_2), 6.35 (br s, 1H, NH), 6.44-6.72 (m 4H aromatic);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 167.2, 152.1, 142.5, 139.7, 116.7, 116.2, 108.0, 59.1, 13.6. Anal. Calcd for $C_{12}H_{11}FN_2O_2S$: C, 54.12; H, 4.16; F, 7.13; N, 10.52; O, 12.02; S, 12.04. Found: C, 54.11; H, 4.17; F, 7.11; N, 10.50; O, 12.01; S, 12.05. m/e= 266.0525

7. ***2-p-Tolylamino-thiazole-4-carboxylic acid ethyl ester***
white solid, mp = 127-130 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.34 (1H), 4.29 (q, *J* = 8.5 Hz, 2H), 1.30 (t, *J* = 6.5 Hz, 3H), 6.82-6.34 (m, 4H), 6.76 (s, 1 H), , 6.35 (br s, 1H, NH), 6.44-6.72 (m 4H aromatic), 2.35 (s, 3H);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 172.0, 167.2, 143.1, 130.5, 127.7, 116.7, 108.0, 59.1, 20.9, 13.6. Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; O, 12.20; S, 12.22. Found: C, 59.01; H, 5.36; N, 10.70; O, 12.18; S, 12.23. m/e= 262.0776

8. ***2-(3-Chloro-phenylamino)-thiazole-4-carboxylic acid ethyl ester***
white solid, mp = 133-136 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.34 (1H), 4.29 (q, *J* = 8.5 Hz, 2H), 1.30 (t, *J* = 6.5 Hz, 3H), 6.95-6.34 (m, 4H), 7.36 (s, 1 H), 6.35 (br s, 1H, NH), 2.35 (s, 3H);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 172.0, 167.2, 148.1, 139.5, 134.4, 130.7, 116.7, 112.0, 59.1, 13.6. Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.92; Cl, 12.52; N, 9.91; O, 11.32; S, 11.34. Found: C, 51.02; H, 3.89; Cl, 12.48; N, 9.92; O, 11.30; S, 11.33. m/e= 282.0230
9. ***2-(2-Chloro-phenylamino)-thiazole-4-carboxylic acid ethyl ester***
white solid, mp = 129-135 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 7.34 (1H), 4.29 (q, *J* = 8.5 Hz, 2H), 1.30 (t, *J* = 6.5 Hz, 3H), 7.02-6.40 (m, 4H), 7.36 (s, 1 H), 6.35 (br s, 1H, NH), 2.35 (s, 3H);^{13}C NMR (125 MHz, DMSO-*d*6) : δ 172.0, 167.2, 147.1, 139.5, 129.4, 127.7, 116.7, 112.0, 108.0, 59.1, 13.6. Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.92; Cl, 12.52; N, 9.91; O, 11.32; S, 11.34. Found: C, 51.03; H, 3.93; Cl, 12.50; N, 9.91; O, 11.29; S, 11.35. m/e= 282.0230
10. ***(3,4-Dimethoxy-phenyl)-(5-methyl-4-phenyl-thiazol-2-yl)-amine***
white solid, mp = 143-145 °C; ^{1}H NMR (500 MHz, DMSO-d6) : δ 7.48 (1H), 2.35 (s, 1H), 1.30 (t, *J* = 6.5 Hz, 3H), 7.22-7.48 (m, 4H), 5.86-5.91 (m, 3H aromatic), 7.36 (s, 1 H), 6.35 (br s, 1H, NH), 3.73 (s, 6H); ^{13}C NMR (125 MHz, DMSO-*d*6) : δ 172.0, 167.2, 148.8, 140.5, 136.4, 129.4, 127.7, 118.4, 118.1, 115.9, 101.0, 108.0, 56.1, 13.2. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; O, 9.80; S, 9.82. Found: C, 66.04; H, 5.52; N, 8.56; O, 9.92; S, 9.85. m/e= 326.1089

11. 3-(5-Methyl-4-phenyl-thiazol-2-ylamino)-benzonitrile
white solid, mp = 110-114 °C; ^{1}H NMR (500 MHz, DMSO-*d*6) : δ 2.35 (s, 1H), 7.22-7.48 (m, 4H), 7.19-6.71 (m, 4H aromatic), 7.36 (s, 1 H), 6.35 (br s, 1H, NH);^{13}C NMR (125 MHz, DMSO-*d*6): δ 172.0, 148.8, 136.5, 129.4, 128.5, 127.7, 122.0, 119.4, 118.4, 116.5, 113.3, 108.0, 13.2. Anal. Calcd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 70.04; H, 4.51; N, 14.45; S, 11.01. m/e= 291.0830

Results and Discussion

The traditional synthesis of 2-aminothiazoles involved Hantzsch condensation from thiourea and α-halocarbonyls and the process need to be ameliorated with some cleaner, greener, easier and effective synthesis of demanding moiety in the medicinal field. The one-pot multicomponent reaction may be utilized in the presence of the base to make some amelioration in the Hantzsch process to make the synthesis of the one of the most desired 2-aminothiazole moiety for the drug designing and synthesis. Ammonia and substituted amines in the presence of the base yields isothiocyanic acid [19] which may be made to react with α-halocarbonyl compound to give thiocyanates [20].

Model reaction was carried out by taking 1 mmol of benzoyl isothiocyanate in round bottom flask and added slowly with 1.5 mmol of aliphatic or aromatic amine and mixed with 1 mol of Triton-B and then with α-bromocarbonyl compound. Now the components of the reaction mixture were stirred at room temperature for 30 min. The organic layer was filtered and dried in the presence of anhydrous Na_2SO_4 and compound was extracted in the presence of ethyl acetate. It was further concentrated on rotatory evaporator and chiller. The purification of the product was done by column chromatography using 1:10 ethyl acetate and n-hexane for elution. The product formed was characterized by NMR, elemental analysis and mass spectra and was found to be (4-Bromo-phenyl)-(4-phenyl-thiazol-2-yl)-amine. The optimization process for the reaction was carried out for the solvent and the phase transfer catalyst. First of all the solvent was optimized and various solvent were taken in consideration to perform the model reaction and we found that the DMSO served the purpose of the reaction well in terms of time and yield (Table 2)

Table 2 Effect of solvents on time and yield of the reaction

S. No	Solvent	Time of the reaction min	% Yield
1	Absent	No reaction	Nil
2	DMSO	30	96
3	DMF	180	45
4	H_2O	>180	10
5	Toluene	120	50

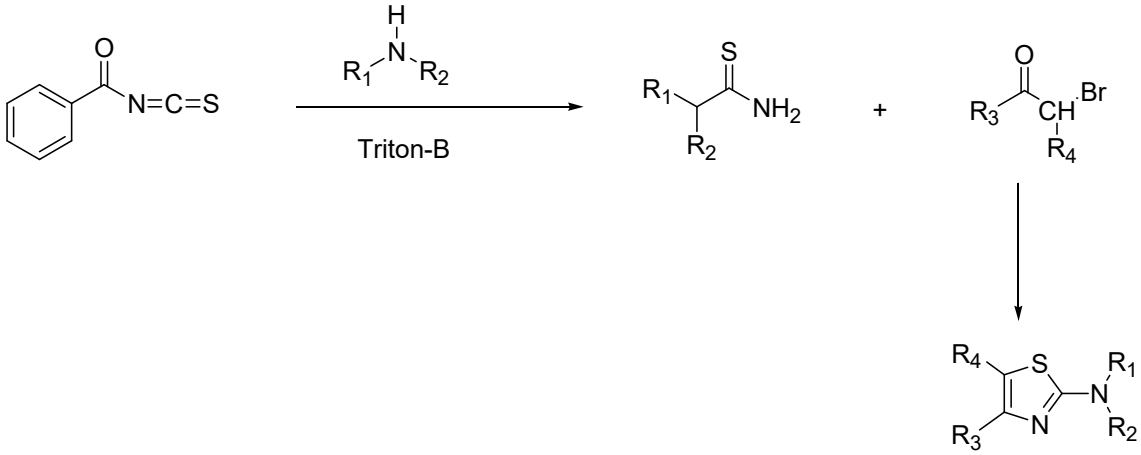
Futher the reaction was optimized for the catalyst. For the suitability of different phase transfer catalyst, we tried many phase transfer catalyst including tetra butyl ammonium chloride (TBAC), crown ether (18 crown 6), tetra n-butyl ammonium bromide (TBAB), Basic resin (Amberlyte IRA 400 in iodide form), tetra n-butyl ammonium hydrogen carbonate (TBAHC), tetra n-butyl ammonium iodide (TBAI), tetra n-butyl ammonium hydrogen sulphate (TBAHS). It was found that Triton-B served 'the best' in getting high yield of the desired 2–aminothiazoles. This reaction was also tried in the absence of the catalyst but no product formed. So it may be said that the reaction could occur only in the presence of catalyst (Table 3)

Table 3 Time and yield of the reaction in different phase transfer catalyst

S N	Phase transfer catalyst	Time in min	% Yield
1	TBAC	>120	40
2	TBAB	>150	50
3	Triton-B	30	96
3	TBAI	>180	60
4	TBAHC	>240	30
5	TBAHS	>240	20
6	Amberlyte IRA 400 (Basic resin)	>240	20
7	18 Crown 6	>240	10
8	Absence of catalyst	No Reaction	0

The anilines as they are less basic than do not undergo protonation completely and may pull the

reaction but they are not as effective as aliphatic amines. The product formed 2-aminothiazole easily clears off HBr. The aliphatic amines due to their higher basicity undergo protonation and so here base like Triton-B need to be added to carry out the reaction and synthesize aminothiazole with aliphatic amines. The developed protocol worked well in case of secondary amines but here precautionary measure need to be taken that the isothiocyanate need to be added in the last to avert the formation of α-aminocarbonyl compound. The steps of the reaction that may have proceeded in the is given below (Scheme 2)



Scheme 2 The Steps of reaction for the synthesis of 2-aminothiazoles

To summarize a novel efficient multicomponent protocol has been developed for the synthesis of 2-aminothiazole which is a privileged moiety in the drug synthesis and may be applied in the case of the synthesis of large number of the aliphatic and aromatic amines based on add them all and wait for the reaction to occur at room temperature.

Conclusion:

A multicompnent cleaner, greener, cheaper, easier and efficient method for the synthesis of 2-amnothiazole has been achieved which may prove very helpful in the synthesis of this prominent moiety in the drug discovery and other field which may be explored further.

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