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Novel Synthesis of 2-Aminothiazoles *via* Fe(III)-Iodine Catalyzed Hantzsch Type Condensation

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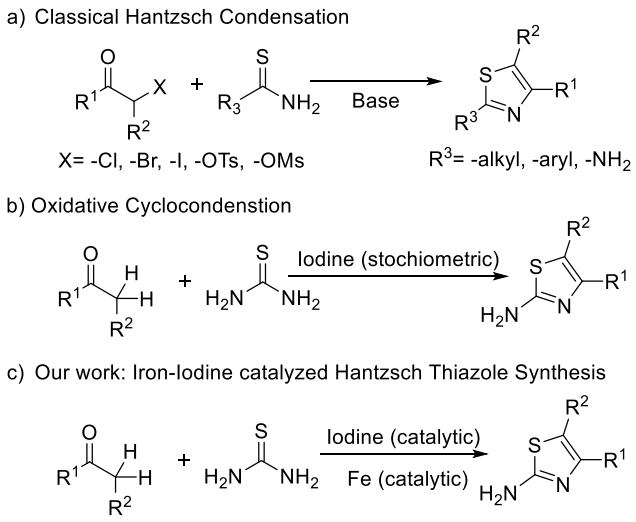
Abstract. A Novel iron-iodine catalyzed one pot synthesis of 2-aminothiazoles from methyl aryl ketones and thiourea is demonstrated. This protocol can be considered as a catalyzed version of the classical Hantzsch aminothiazole synthesis as it enables the in situ generation of α-iodoketones in the reaction medium using catalytic amount of iodine leading to Hantzsch condensation with thiourea. The supply of iodine for multiple catalytic cycles is ensured by using catalytic amounts of iron as it enables iodide to iodine oxidation. The generality of this protocol is also well established in this manuscript by synthesizing a variety of 2-aminothiazoles from different ketones and thiourea.

Keywords: aminothiazole; catalysis ; Hantzsch reaction ; iodine ; iron

1. Introduction

2-Aminothiazoles are very important heterocycles known for their wide spectrum of biological activities. Many drugs are available in the market nowadays containing aminothiazole core including potent CNS active agents. Some of the examples are Cefdinir (Anti-biotic), [1] Famotidine (Histamine-2 blocker), [2] Abafungin (Anti-microbial), [3] Fanetizole (Anti-inflammatory), [4] Pramipexole (Treatment of Parkinson's disease) [5] etc. The known methods for the synthesis of these molecules include **i)** from acetophenone and thiourea mediated by strong oxidizing agents [6] like Sulfuryl chloride, Sulfur trioxide, Nitric acid, Sulfur, halogen [7] etc. **ii)** from *α*-diazoketone and thiourea [8] **iii)** from primary amines and halo-thiocyanatoalkenes [9] **iv)** from alkynes and thiourea [10] **v)** from *α*-nitro epoxides and thiourea [11] **vi)** from vinyl azides with thiocyanate [12] etc. Hantzsch condensation [13] is a well explored methodology which involves reaction of thioamides with *α*-haloketones to afford aminothiazoles. It was first reported in 1887 **(Scheme 1a)** and later underwent many developments. The major modification was the use of ketone along with stoichiometric amounts of iodine instead of haloketones to afford aminothiazoles on reaction with thiourea *i. e.* Oxidative cyclocondenstion [14] **(Scheme 1b)**. This protocol was superior over **Scheme 1a,** since α-haloketones were less commercially available and possess lachrymatory nature. Use of stoichiometric amounts of iodine often resulted in the formation of unwanted by-products leading to complex separation procedures. Our group's continued interest in developing transition metal catalyzed versions of classic name reactions [15] made us investigate a similar scope in the case of Hantzsch reaction also. By using a catalytic amount of iron and iodine, we could develop a protocol that employs acetophenone and thiourea as the starting materials to afford 2-aminothiazoles **(Scheme 1c)**. We propose that *via* repeated iron-iodine-involved catalytic cycles, *in situ* generation of *α*-iodoacetophenone from acetophenone could take place in the reaction mixture which would react with thiourea to afford the product. The protocol is very useful towards the synthesis of a variety of 2-aminothiazoles from 2-methylketones and thiourea under much milder conditions.

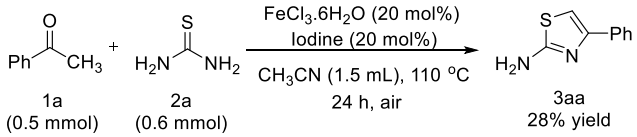


Scheme 1. Scheme 1: a) Classical Hantzsch condensation between α-halo ketone and thioamide; b) Oxidative cyclocondensation using stoichiometric amounts of iodine c) Our modification leading to catalytic version of Hantzsch condensation.

Recently many green approaches were emerged in the area of Hantzsch reaction to afford 2-aminothiazoles. [16] Our methodology will be a new addition to these protocols as it uses environmentally benign PEG-400 as the solvent along with iron/iodine catalytic system.

2. Result and Discussion

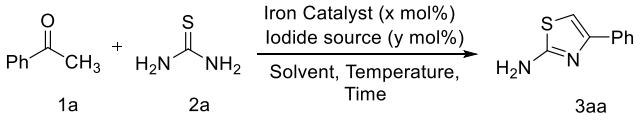
The optimization studies were began with a trial reaction involving acetophenone, **1a** (0.5 mmol) and thiourea **2a** (0.6 mmol) as the substrates. Ferric chloride hexahydrate and iodine were used as the catalysts. All the reagents were stirred at 110 ^{o}C in a sealed tube using CH_3CN as the solvent (**Scheme 2**). The progress of the reaction was monitored using TLC and the reaction mixture was quenched after 24 hours and extracted using ethyl acetate. The residue obtained after concentration of the solvent was purified using column chromatography (Hexane-EtOAc) to furnish the desired 4-phenylthiazol-2-amine in 28 % yield.



Scheme 2: Iron catalyzed Hantzsch-type reaction between acetophenone and thiourea.

Once the trial reaction was found proceeding in the desired way, further studies were carried out by varying the iron salt, iodine source, solvent, time, temperature and the catalyst loading **(Table 1).**

Table 1: Optimization studies



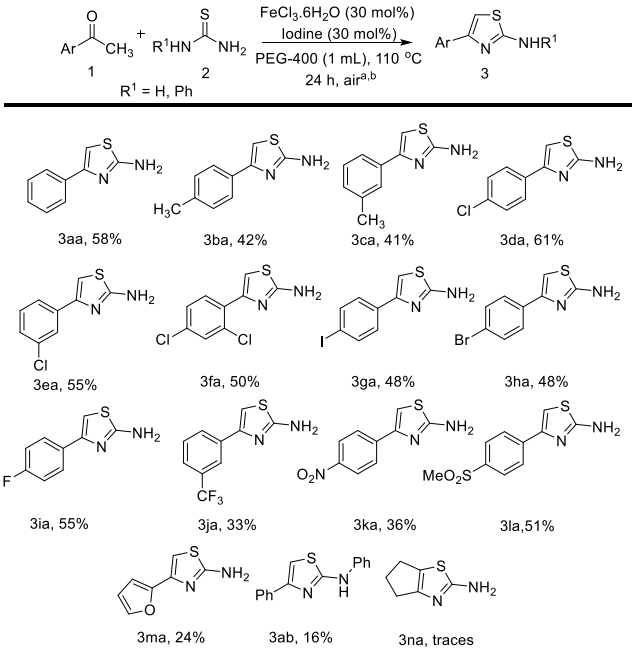
Sl No.	Iron catalyst (mol%)	Iodide source (mol%)	Solvent	Temp. (^{o}C)	Time (h)	Yield (%)[a, b]
1	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	CH_3CN	110	24	28
2	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	CH_3CN	80	24	18
3	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	CH_3CN	130	24	traces
4	$FeCl_3.6H_2O$ (30 mol%)	KI (30 mol%)	CH_3CN	110	24	24
5	$Fe(NO_3)_3.9H_2O$ (20 mol%)	I_2 (20 mol%)	CH_3CN	110	24	traces
6	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	DME	110	24	25
7	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	THF	110	24	traces
8	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	DMF	110	24	30
9	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	DMSO	110	24	traces
10	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	^{t}BuOH	110	24	38
11	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	EtOH	110	24	traces
12	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	Toluene	110	24	traces
13	$FeCl_3.6H_2O$ (20	I_2 (20 mol%)	NMP	110	24	28

	mol%)					
14	$FeCl_3.6H_2O$ (20 mol%)	I_2 (20 mol%)	PEG-400	110	24	41
15	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	PEG-400	110	24	58
16	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	CH_3CN	110	24	48
17	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	DMF	110	24	38
18	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	^{t}BuOH	110	24	38
19	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	H_2O	110	24	trace s
20	$FeCl_3.6H_2O$ (50 mol%)	I_2 (50 mol%)	PEG-400	110	24	43
21	$FeCl_3.6H_2O$ (20 mol%)	I_2 (30 mol%)	PEG-400	110	24	40
22	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	PEG-400	110	19	43
23	$FeCl_3.6H_2O$ (30 mol%)	I_2 (30 mol%)	PEG-400	110	30	56
24	$FeCl_3$ Anhydrous (30 mol%)	I_2 (30 mol%)	PEG-400	110	24	53
25	$Fe(OTf)_2$ (30 mol%)	I_2 (30 mol%)	PEG-400	110	24	42
26	-	I_2 (30 mol%)	PEG-400	110	24	35
27	$FeCl_3.6H_2O$ (30 mol%)	-	PEG-400	110	24	trace s
28	-	-	PEG-400	110	24	nd

[a] **Reaction Conditions: 1a** (0.5 mmol), **2a** (0.6 mmol), Fe catalyst (20-50 mol%), Iodide source (20-50 mol%), Solvent, 80-110 ^oC, 19-30 h; [b] Isolated yield. nd= not detected.

The first parameter we modified in comparison to the trial reaction **(Entry 1)** was the temperature by keeping all the other parameters the same. A decrease or an increase in the temperature was found to cause the yield to decrease or the amount of product become traces **(Entry 2&3)**. The use of $Fe(NO_3)_3.9H_2O$ instead of $FeCl_3.6H_2O$ or KI instead of I_2 also didn't improve the yields **(Entry 4&5)**. Influence of different solvents in the reaction was then examined. Solvents including tetrahydrofuran, dimethylsulfoxide and ethanol were ineffective **(Entry 7, 9&11)**. Similar was the result in the case of toluene **(Entry 12)**. NMP gave only 28% of the yield while ^{t}BuOH and PEG-400 gave improved yields of 38% and 41% respectively **(Entry 13, 10&14)**. Upon increasing the quantities of both $FeCl_3.6H_2O$ and I_2 from 20 mol% to 30 mol%, the yields got increased. In the case of acetonitrile, the yield was improved to 48% **(Entry 16)**. Similarly PEG-400 has furnished 58% of the product and was found to be the best solvent among the all **(Entry 15)**. Thus we have chosen PEG-400 as the solvent for the subsequent studies. A decrease in the duration of the reaction from 24 hours to 19 hours resulted in lowering of the yield **(Entry 22)**. However, an increase of reaction time did not make any impact on the yield **(Entry 23)**. A change in the catalytic loading from 30 mol% to 50 mol% resulted in the decrease of the yield **(Entry 20)**. We also changed the [Fe]:I_2 ratio to 1:1.5, which offered a reduced yield of 40% **(Entry 21)**. The catalytic activity of a ferrous salt was also tested to afford 42% of the product **(Entry 25)**. When the reaction was carried out in the absence of iron the yield was only 35% **(Entry 26)**. The use of iron as the sole catalyst only delivered traces of the product **(Entry 27)**. From all these results, we have concluded **Entry 15** as the optimum condition and proceeded with the substrate scope studies.

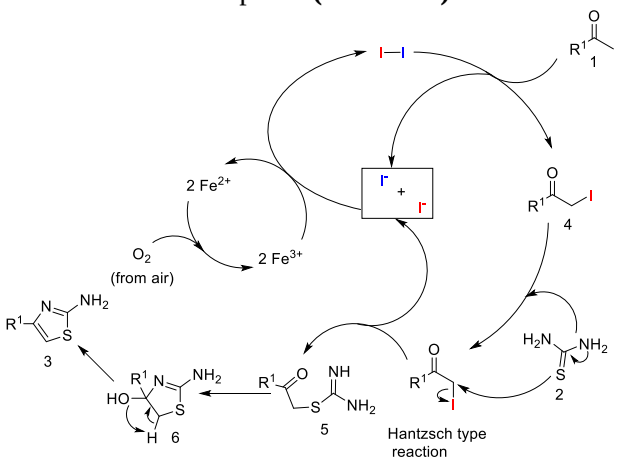
The generality of this protocol was well studied later with a variety of ketones and thiourea. Electron withdrawing as well as electron donating groups were well tolerated under the reaction conditions **(Scheme 3)**. Electronic nature of the substituents on the arylketones did not make any direct correlation with the yields. Among the halo ketones, 4-chloroacetophenone offered the highest yield (**Scheme 3, 3da**) whereas 4-iodoacetophenone afforded the lowest (**Scheme 3, 3ga**). In the case of heterocyclic ketone, the yield was very low (**Scheme 3, 3ma**). Cyclopentanone furnished 5,6-dihydro-4H-cyclopenta[*d*]thiazol-2-amine as the product, *albeit* in very low amounts (**Scheme 3, 3na**). N-Phenylthiourea (**Scheme 3, 3ab**) has provided only 16% of the product, presumably due to steric effects.



[a] Reaction Conditions: **1** (0.5 mmol), **2** (0.6 mmol), $FeCl_3.6H_2O$ (30 mol%), iodine (30 mol%), PEG-400, 110 °C, 24 h; [b] Isolated yields.

Scheme 3: Substrate scope studies

Finally we propose a mechanism for this transformation. It initiates with the *in situ* generation of the α-iodoketones, **4** from the methyl ketones, which then undergoes Hantzsch type condensation with thiourea to afford the product (**4 to 3**). There are two iodide ions being liberated during each catalytic cycle, which are oxidized back to the molecular iodine by Fe^{3+}. The Fe^{2+} ion formed during this step is converted to the active Fe^{3+} ion by the oxygen present in the aerobic atmosphere **(Scheme 4)**.



Scheme 4: The proposed mechanism

3. Conclusion

We have developed, a catalyzed version of Hantzsch-type reaction towards the synthesis of 2-aminothiazoles from methyl aryl ketones and thiourea. The protocol employs a catalytic system composed of FeCl3.6H2O and iodine in environmentally benign PEG-400 as the solvent. The major advantages of this methodology over the existing protocols are that it avoids α-prefunctionalization of ketones, use of strong oxidizing agents and only require catalytic amounts of iodine.

4. Experimental Section

4.1. General Remarks

Ferric chloride hexahydrate, Thiourea and Potassium iodide were purchased from Sigma Aldrich, Germany. The Iodine resublimed, Toluene, NMP and *t*-Butanol were provided by SRL chemicals, India. Anhydrous Ferric chloride and ferric nitrate nonahydrate were purchased from Merck Specialities Pvt. Ltd. India. Methanol, DMF and acetonitrile were the products of Sigma Aldrich. Other solvents including PEG-400 and Ethanol were respectively purchased from Spectrochem, India and Hayman. The ketones used were manufactured by Sigma Aldrich, Alfa Aesar and SRL, India. Solvents used for column chromatography were purchased from Thermofischer scientific and distilled before use. The NMR spectra were recorded using a Bruker-500 MHz NMR spectrometer instrument. The chemical shift values were reported in 'ppm' relative to TMS (1H) and CDCl3 (13C) as internal standards. Coupling constants (J) were stated in Hertz (Hz). The GC-MS and HRMS were recorded respectively on Agilent and XEVO G2 Q-TOF (Waters) mass spectrometers. Column chromatography was carried out using 100-200 mesh silica gel from SRL chemicals. Thin Layer Chromatography was carried out using Merck SilicaGel 60/UV254 plates and the spots were detected using either UV fluorescence or by Iodine chamber.

4.2. *General procedure for the Synthesis of 2-Aminothiazoles*

An oven dried sealed tube containing a magnetic stirring bar was charged with the ketone (0.50 mmol), thiourea (0.60 mmol), $FeCl_3.6H_2O$ (30 mol%), Iodine (30 mol%) and PEG-400 (1 mL). The tube was tightly closed and the contents were stirred at 110 °C for 24h in an oil bath. Upon completion, the reaction mixture was extracted with EtOAc (15 mLx3 times). The extract was dried over dry Na_2SO_4 and the solvent was removed in vaccuo using a rotatory evaporator. The obtained residue was later purified by column chromatography (Silica 60-120 mesh) using hexane-EtOAc mixture.

4.3. Compound Characterization Data

4-Phenylthiazol-2-amine (3aa);[17] Chemical Formula: $C_9H_8N_2S$; Appearance: White Solid; Yield: 51 mg (58%); MP: 150-152 °C (lit. 151–153 °C)[17]; **FT-IR** (neat): 3433, 3248, 3153, 3113, 2921, 1689, 1596, 1515, 1329, 1038, 1022, **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 5.30 (s, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.5, 151.3. 134.7, 128.6, 127.8, 126.0, 102.8; **GC-MS** (EI): *m/z* 176 (M^+).

4-(*p*-Tolyl)thiazol-2-amine (3ba);[18] Chemical Formula: $C_{10}H_{10}N_2S$; Appearance: White Solid; Yield: 40 mg (42%); MP: 128-130 °C (lit. 124-126 °C)[18]; **FT-IR** (neat): 3452, 3297, 3117, 2757, 1634, 1537, 1331, 1035, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.67 (s, 1H), 5.02 (s, 2H), 2.36 (s, 3H); **^{13}C**

NMR ($CDCl_3$, 125 MHz) δ 167.2, 151.6. 137.7, 132.2, 129.4, 126.1, 102.3, 21.4; **GC-MS** (EI): *m/z* 190 (M^+).

4-(*m*-Tolyl)thiazol-2-amine (3ca);[17] Chemical Formula: $C_{10}H_{10}N_2S$; Appearance: White Solid; Yield: 39 mg (41%); MP: 84-86 °C (lit. 88-91 °C)[17]; **H NMR** (DMSO-d6, 500 MHz) δ 8.71 (bs, 2H), 7.55 (s, 1H), 7.51 (d, *J* = 10.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 2.29 (s, 3H); **^{13}C NMR** (DMSO-d6, 125 MHz) δ 169.2, 139.6, 137.4, 128.9, 128.6, 128.0, 125.3, 121.9, 101.3, 20.1; **GC-MS** (EI): *m/z* 190 (M^+).

4-(4-Chlorophenyl)thiazol-2-amine (3da);[17] Chemical Formula: $C_9H_7ClN_2S$; Appearance: White Solid; Yield: 64 mg (61%); MP: 165-167 °C (lit. 161-162 °C)[17]; **FT-IR** (neat): 3435, 3279, 3108, 2757, 1631, 1532, 1327, 1036, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 10.0 Hz, 2H), 6.71 (s, 1H), 5.05 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.4, 150.4, 133.6, 133.3, 128.9, 127.4, 103.4; **GC-MS** (EI): *m/z* 210 (M^+).

4-(3-Chlorophenyl)thiazol-2-amine (3ea);[18] Chemical Formula: $C_9H_7ClN_2S$; Appearance: White Solid; Yield: 58 mg (55 %); MP: 128-130 °C (lit. 126-128 °C)[18]; **FT-IR** (neat): 3310, 3127, 1632, 1517, 1337, 1050, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.69 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.23-7.17 (m, 2H), 6.66 (s, 1H), 5.20 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.6, 150.0, 136.5, 134.7, 130.0, 127.8, 126.3, 124.1, 104.0; **GC-MS** (EI): *m/z* 210 (M^+).

4-(2,4-Dichlorophenyl)thiazol-2-amine (3fa);[19] Chemical Formula: $C_9H_6Cl_2N_2S$; Appearance: White Solid; Yield: 61 mg (50%); MP: 157-159 °C (lit. 161-163 °C)[19]; **FT-IR** (neat): 3451, 3275, 3107, 1630, 1536, 1335, 1025, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.81 (d, *J* = 10.0 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.08 (s, 1H), 5.02 (s, 2H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 166.2, 146.6, 133.7, 132.5, 132.2, 132.0, 130.3, 127.3, 108.8; **GC-MS** (EI): *m/z* 244 (M^+).

4-(4-Iodophenyl)thiazol-2-amine (3ga);[18] Chemical Formula: $C_9H_7IN_2S$; Appearance: Pale Yellow Solid; Yield: 73 mg (48 %); MP: 167-169 °C (lit. 176-177 °C)[18]; **FT-IR** (neat): 3420, 3279, 3107, 1627, 1530, 1326, 1034, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.74 (s, 1H), 5.01 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.4, 150.4, 137.8, 134.2, 127.9, 103.6, 93.3; **GC-MS** (EI): *m/z* 302 (M^+).

4-(4-Bromophenyl)thiazol-2-amine (3ha);[18] Chemical Formula: $C_9H_7BrN_2S$; Appearance: Pale Yellow Solid; Yield: 61 mg (48%); MP: 184-186 °C (lit. 179-181 °C)[18]; **FT-IR** (neat): 3426, 3279, 3109, 2757, 1634, 1531, 1334, 1035, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 5.02 (s, 2H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.4, 150.4, 133.8, 131.8, 127.7, 121.8, 103.5; **GC-MS** (EI): *m/z* 254 (M^+).

4-(4-Fluorophenyl)thiazol-2-amine (3ia);[18] Chemical Formula: $C_9H_7FN_2S$; Appearance: White Solid; Yield: 53 mg (55%); MP: 100-102 °C (lit. 103-104 °C)[18]; **FT-IR** (neat): 3469, 3306, 3126, 2767, 1639, 1533, 1338, 1037, **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.76-7.73 (m, 2H), 7.08-7.04 (m, 2H), 6.65 (s, 1H), 5.02 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.3, 163.6, 161.6, 150.5, 140.1, 131.1 (2 peaks), 127.9, 127.8, 115.7, 115.5, 102.6 (2 peaks); **GC-MS** (EI): *m/z* 194 (M^+).

4-(3-(Trifluoromethyl)phenyl)thiazol-2-amine (3ja);[20] Chemical Formula: $C_{10}H_7F_3N_2S$; Appearance: White Solid; Yield: 40 mg (33%); MP: 103-105 °C; **^{1}H NMR** (DMSO-d6, 500 MHz) δ 8.13 (s, 1H), 8.09 (bs, 1H), 7.59 (bs, 2H), 7.25 (bs, 1H), 7.18 (s, 2H); **^{13}C NMR** (DMSO-d6, 125 MHz) δ 167.7, 147.2, 134.9, 130.2, 130.1, 130.0, 129.7, 129.6, 129.5, 128.0, 125.8, 124.0 (2 peaks), 123.7, 122.4 (2 peaks), 121.5; **GC-MS** (EI): *m/z* 244 (M^+).

4-(4-Nitrophenyl)thiazol-2-amine (3ka);[17] Chemical Formula: $C_9H_7N_3O_2S$; Appearance: Yellow powder; Yield: 40 mg (36 %); MP: 284-286 °C (lit. 285-286 °C)[17]; **FT-IR** (neat): 3394, 3302, 3145, 3114, 1638, 1592, 1536, 1410, 1317, 1036, **^{1}H NMR** (DMSO-d6, 400 MHz) δ 8.23 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.25 (s, 2H); **^{13}C NMR** (DMSO-d6, 100 MHz) δ 168.6, 147.6, 146.0, 140.7, 126.3, 124.0, 106.6; **GC-MS** (EI): *m/z* 222 ($M+H^+$).

4-(4-(Methylsulfonyl)phenyl)thiazol-2-amine (3la);[21] Chemical Formula: $C_{10}H_{10}N_2O_2S_2$; Appearance: White powder; Yield: 65 mg (51 %); MP: 225-227 °C; **FT-IR** (neat): 3417, 3278, 3108, 1646, 1532, 1280, 1035, **^{1}H NMR** (DMSO-d6, 400 MHz) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.18 (s, 2H), 3.22 (s, 3H); **^{13}C NMR** (DMSO-d6, 100 MHz) δ 168.5, 148.2, 139.4, 138.8, 127.4, 126.0, 105.2, 43.6; **MS-MS** (EI): *m/z* 255 ($M+H^+$).

4-(Furan-2-yl)thiazol-2-amine (3ma);[22] Chemical Formula: $C_7H_6N_2OS$; Appearance: White Solid; Yield: 20 mg (24%); MP: 112-114 °C (lit. 115 °C) [23]; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 6.69 (s, 1H), 6.62 (d, *J* = 3.5 Hz, 1H), 6.44 (m, 1H), 5.03 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.6, 150.4, 143.0, 142.0, 111.5, 106.5, 102.5; **GC-MS** (EI): *m/z* 166 (M^+).

N,4-Diphenylthiazol-2-amine (3ab);[24] Chemical Formula: $C_{15}H_{12}N_2S$; Appearance: Slightly yellow Solid; Yield: 20 mg (16 %); MP: 138-140 °C (lit. 133-135 °C)[23]; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.86 (d, *J* = 10.0 Hz, 2H), 7.42-7.30 (m, 8H), 7.08 (t, *J* = 7.0 Hz, 2H), 6.84 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 164.5, 151.5, 140.4, 134.7, 129.6, 128.8, 128.0, 126.2, 123.1, 118.3, 102.0; **GC-MS** (EI): *m/z* 252 (M^+).

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References

[1] P. D. R. Guay, *Clin Ther.* **2002**, *24*, 473–489.

[2]. L. Laine, A. J. Kivitz, A. E. Bello, A. Y. Grahn, A. Y Schiff, A. S. Taha, *Am. J. Gastro.* **2012**, *107*, 379–386.

[3]. C. Borelli, M. Schaller, M. Niewerth, K. Nocker, B. Baasner, D. Berg, R. Tiemann, K. Tietjen, B. Fugmann, S. Lang-Fugmann, H. C. Korting, *Chemotherapy* **2008**, **54**, 245–259.

[4]. J. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org Proc Res Dev.* **2013**, *17*, 1183-1191.

[5]. C. De Battista, H. B. Solvason, J. A. Breen, A. F. Schatzberg, *J. Clin. Psychopharmacol.* **2000**, *20*, 274–275.

[6]. R. M. Dodson, L. C. King, *J. Am. Chem. Soc.* **1946**, *68*, 871–871.

[7]. a) R. M. Dodson, L. C. King, *J. Am. Chem. Soc.* **1945**, *67*, 2242–2243. b) L. C. King, R. J. Hlavacek, *J. Am. Chem. Soc.* **1950**, *72*, 3722–3725.

[8].L. C. King, F. Miller, *J. Am. Chem. Soc.* **1949**, *71*, 367–368.

[9]. M. Giffard, J. Cousseau, *Tetrahedron Lett.* **1983**, *24*, 5085–5088.

[10] B. Madhav, S. N. Murthy, B.S.P. Anil Kumar, K. Ramesh, Y.V.D. Nageswar, *Tetrahedron Lett.* **2012**, *53*, 3835-3838.

[11] D. Zhao, S. Guo, X. Guo, G. Zhang, Y. Yu, *Tetrahedron* **2016**, *72*, 5285-5289.

[12] B. Chen, S. Guo, X. Guo, G. Zhang, Y. Yu, *Org Lett.* 2015, *17*, 4698-4701.

[13]. a) A. Hantzsch, J. H. Weber, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118-3132. b) G. W. Kabalka, A. R. Mereddy, *Tetrahedron Lett.* **2006**, *47*, 5171–5172. c) M. M. Heravi, P. Nargess, Y. S. Beheshtiha, B. Baghernejad, *Synth. Commun.* **2011**, *41*, 579–582. d) M. Kidwai, D. Bhatnagar, P. Mothsra, A. K. Singh, S. Dey, *J. Sulfur. Chem.* **2009**, *30*, 29-36.

[14]. a) T. M. Potewar, S. A. Ingale, K. V. Srinivasan, *Tetrahedron* **2008**, *64*, 5019-5022. b) N. Narender, M. S. Reddy, V. P. Kumar, V. P. Reddy, Y. V. D. Nageswar, K. R. Rao, *J. Org. Chem.* **2007**, *72*, 1849-1851. c) H. Bouherrou, A. Saidoun, A. Abderrahmani, L. Abdellaziz, Y. Rachedi, F. Dumas, A. Demenceau, *Molecules* **2017**, *22*, 757-759. d) Y, -P. Zhu, J. -J. Yuan, Q. Zhao, M. Lian, Q. –H. Gao, M. –C. Liu, Y. Yang, A. –X. Wu, *Tetrahedron* **2012**, *68*, 173-178.

[15]. S. M. Ujwaldev, K. R Rohit, N. A. Harry, G. Anilkumar, *Tetrahedron Lett.* **2019**, *60*, 150950-150954.

[16] a) D. C. Castillo, R. M. Carballo, J. A. Tzec-Interián, G. J. Mena-Rejón, *Tetrahedron Lett.* **2012**, *53*, 3934–3936. b) J. Safari, Z. A. -Jazini, Z. Zarnegar, M. Sadeghi, *Catal. Commun.* **2016**, *77*, 108-112.

[17] J. Safari, M. Sadeghi, *Monatsh Chem.* **2017**, *148*, 745-749.

[18]. M. Chunhua, Y. Miao, M. Zhao, P. Wu, J. Zhou, Z. Li, X. Xie, W. Zhang, *Tetrahedron* **2018**, *74*, 3602-3607.

[19]. D. Zhu, J. Chen, H. Xiao, M. Liu, J. Ding, H. Wu, *Synth. Commun.* **2009**, *39*, 2895-2906.

[20]. K. Ran, C. Gao, H. Deng, Q. Lei, X. You, N. Wang, Y. Shi, Z. Liu, W. Wei, C. Peng, L. Xiong, K. Xiao, L. Yu, *Bioorg. Med. Chem.* **2016**, *26*, 3669-3674.

[21]. G. W. Kabalka, R. M. Arjun, *Tetrahedron Lett.* **2006**, *47*, 5171-5172.

[22]. P. Z. Yan, Y. P. Zhu, J. J. Yuan, Q. Zhao, M. Lian, Q. H. Gao, M. C. Liu, Y. Yang, A. X. Wu, *Tetrahedron* **2012**, *68*, 173-178.

[23]. S. P. Singh, R. Naithani, R. Aggarwal, Om Prakash, *Synth. Commun.* **1998**, *28*, 2371-2378.

[24]. A. Mishra, M. Srivastava, P. Rai, S. Yadav, B. P. Tripathi, J. Singh, J. Singh, *RSC Adv.* **2016**, *6*, 49164-49172.

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