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Microwave assisted multicomponent reaction: An environmentally benign protocol for the synthesis of substituted imidazo[2,1-*b*]thiazole-2-carbohydrazide derivatives under solvent free condition

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ABSTRACT

The present report describes a microwave assisted convenient and efficient protocol for the synthesis of new 6-(4-substituted-phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide derivatives. The current method holds a tag of green synthesis by virtue of catalyst and solvent free media. Moreover, the procedure offers excellent yield and purity of the products under mild condition compared with conventional method.

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1. Introduction

In the last decade, synthetic chemists have oriented towards a sound interest in the development of one-pot multi-component reactions (MCRs), in order to develop libraries of diver's heterocyclic compounds. The high efficiency, conveniences and atom economy are the reticular properties of MCRs in comparison with multistage procedure [1-4].These properties of the MCRs are always woven to the green chemistry protocol, which fascinated the researchers to synthesis various bioactive compounds using MCRs [5-9].

Microwave assisted organic synthesis had become compelling and prominent approach in synthetic chemistry because, it meets various scientific challenges coming from traditional synthetic procedure such as consumption of conventional organic solvents [10], prolonged reaction time[11], high cost of catalyst and low selectivity of the product [12]. MCRs incorporated with microwave assisted synthesis enhances reaction rate [13-15] and product yield [16-18] with high atom efficiency [19,20] proving themselves in accordance with the green chemistry protocols [21-25]. Synthesis of biologically important pharmacophore by solvent and catalyst free microwave assisted MCRs results in achievement to decreased cost and time required for reaction.

Catalyst plays a vital role in synthesis by enhancing the rate of reaction without making any change in product [26]. Almost all the time the catalyst was thrown out after the completion of the reaction. This may be incorporated with the use of eco-friendly solvents, as they are safer to handle and gives desired product, purity and good yield [27,28]. Despite of this use of solvent and catalyst may interrupt the environment by consuming natural resources. Thus MCRs designed without the use of catalyst and solvents accompanied with microwave assisted synthesis are most welcome and adapted in the synthetic field.

Hydrazides were perceived as crucial starting material of wide range of derivatives applied in pharmaceutical industries. Hydrazides have been studied comprehensively because of their diverse chemical reactivity and broad spectrum of biological activity.

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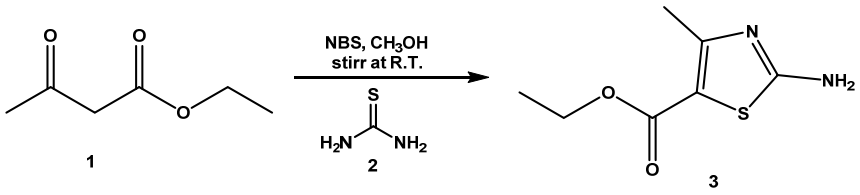
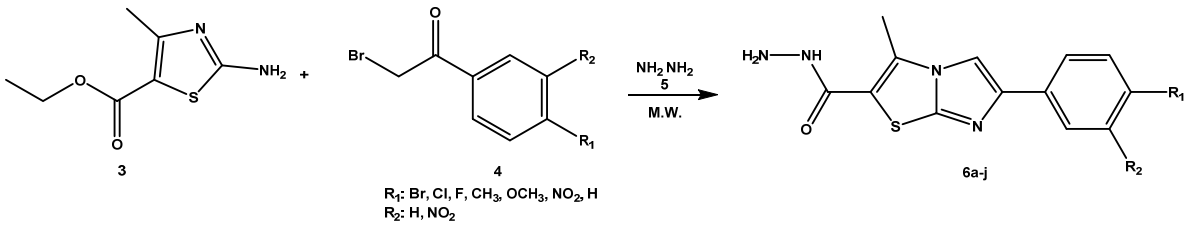


Scheme 1



Scheme 2

Numbers of hydrazide derivatives are known to possess anti-tubercular [29,30], antifungal [31], antibacterial [32,33], antihelmintic [34], anticonvulsant [35] and anti HIV activities [36].

These facts create vital interest of researcher to develop a competent method for their synthesis. As a part of our efforts for the development of green methodology for synthesis of biologically important scaffolds [37-44], herein we report microwave assisted MCR for synthesis of new 6-(4-substituted-phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide derivatives.

2. Experimental

2.1. Material and methods

All reagents and chemicals were used laboratory grade and purified prior to use. Melting points of all synthesized compounds were recorded in open capillary tubes and are uncorrected. IR spectra were recorded in KBr pellets on a FT-IR Shimadzu spectrophotometer, and ^{1}H NMR spectra in dimethylsulfoxide solvent were scanned on an AVANCE 300/400 MHz spectrometer using TMS as an internal standard. The MS were recorded on an EI-Shimadzu-GC-MS spectrometer. Elemental analysis was carried out on a Carlo Erba 106 Perkin-Elmer model 240analyzer.

2.2. General procedure for synthesis of 6-(4-substituted-phenyl)-3-methylimidazo[2,1-b]thiazole-2-carbohydrazide

2.2.1. Method A: Conventional synthesis

For the synthesis of the 6-(4-substituted-phenyl)-3-methylimidazo[2, 1-*b*]thiazole-2-carbohydrazide derivatives, ethyl 2-amino-4-methylthiazole-5-carboxylate (1 mmol) and substituted phenacyl bromide (1 mmol) was taken in round bottom flask and reflux for 3 hours at 100-130°C. Reaction mass was examined by thin-layer chromatography (TLC) clearly reflect the formation of intermediate ethyl 6-(4-substituted-phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carboxylate. Thenceforth in the same pot excess of hydrazine hydrate was added and the reaction mass was further refluxed for 2 to 3 hours, at the same temperature. Finally, the reaction mixture was poured on crushed ice to form the final 6-(4-substituted-phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide derivatives as a solid (Scheme 1 - 3).

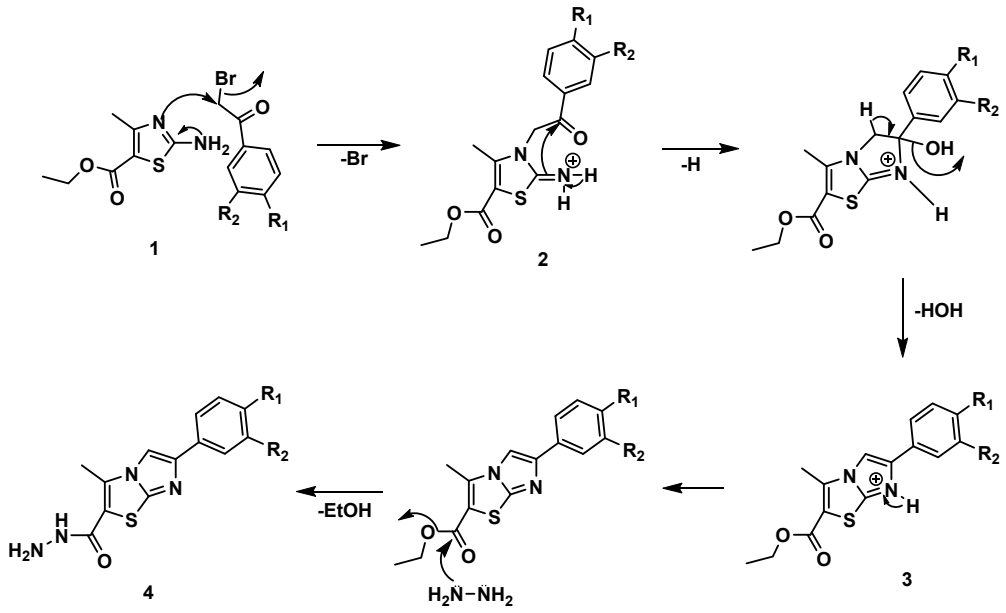
2.2.2. Method B: Microwave assisted synthesis

For the synthesis of target compound ethyl 2-amino-4-methylthiazole-5-carboxylate (1 mmol) and substituted phenacyl bromide (1 mmol) was taken in open vial and placed under microwave radiation at 110 to 120 °C. At regular interval of 1 minute, product was examined by TLC using petroleum ether and ethyl acetate as eluent (8:2 ratios). Completion of reaction is confirmed by TLC after 2 to 3 minutes. After this subsequently few drops of hydrazine hydrate was added in same vessel and again the reaction mass was radiated by microwave radiation at 120 °C after 2 to 3 minutes TLC shows the completion of reaction. The formed semisolid reaction mixture was poured on crushed ice and formed solid was filtered, dried and recrystallized with aqueous acetic acid. Product is observed to be in good to excellent yield. The reaction is shown in Scheme 1 and 2.

6-(4-Bromophenyl)-3-methylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6a**): Color: Pale yellow. Yield: 80%. M.p.: 110-112 °C. FT-IR (KBr, ν, cm^{-1}): 3330 (NH_2), 3247 (NH), 1670 (C=O)(amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.78 (s, 3H, CH_3), 4.55 (s, 2H, NH_2), 7.50-7.53 (dd, 2H, Ar-H, *J* = 7.6 Hz), 8.00-8.12 (dd, 2H, Ar-H, *J* = 8 Hz), 8.54 (s, 1H, CH), 9.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 155, 150, 140, 136, 130, 128, 107. MS (EI, *m/z* (%)): 351 (M^+). Anal. calcd. for $C_{13}H_{11}BrN_4OS$: C, 44.46; H, 3.16; N, 15.95. Found: C, 44.41; H, 3.19; N, 15.91%.

6-(4-Chlorophenyl)-3-methylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6b**): Color: Yellow. Yield: 75%. M.p.: 105-107 °C. FT-IR (KBr, ν, cm^{-1}): 3225 (NH_2), 3200 (NH), 1669 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.69 (s, 3H, CH_3), 4.55 (s, 2H, NH_2), 7.41-7.43 (dd, 2H, Ar-H, *J* = 7.5 Hz), 7.85-7.87 (dd, 2H, Ar-H, *J* = 7.5 Hz), 8.33 (s, 1H, C_5CH), 9.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.02, 146.59, 145.71, 132.55, 131.81, 130.96, 128.41, 126.39, 108.26, 12.91. MS (EI, *m/z* (%)): 307 (M^+). Anal. calcd. for $C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; N, 18.26. Found: C, 50.88; H, 3.63; N, 18.23%.

6-(4-Fluorophenyl)-3-methylimidazo[2,1-b]thiazole-2-carbohydrazide (**6c**): Color: Pale white. Yield: 75%. M.p.: 111-113 °C. FT-IR (KBr, ν, cm^{-1}): 3333 (NH_2), 3300 (NH), 1678 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.00 (s, 3H, CH_3), 5.33 (s, 2H, NH_2), 7.44-7.46 (dd, 2H, Ar-H, *J* = 7.0 Hz), 8.55-8.57 (dd, 2H, Ar-H, *J* = 8.0 Hz), 8.01 (s, 1H, C_5 CH), 9.66 (s, 1H, NH).



Scheme 3

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 166.01, 149.59, 143.71, 130.54, 131.81, 129.95, 125.40, 126.30, 100.25, 12.90. MS (EI, *m/z* (%)): 290 (M^+). Anal. calcd. for $C_{13}H_{11}FN_4OS$: C, 53.78; H, 3.82; N, 19.30. Found: C, 53.74; H, 3.83; N, 19.34%.

3-Methyl-6-(p-tolyl)imidazo[2, 1-b]thiazole-2-carbohydrazide (**6d**): Color: Pale yellow. Yield: 77%. M.p.: 100-102 °C. FT-IR (KBr, ν, cm^{-1}): 3200 (NH_2), 3000 (NH), 1660 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.11 (s, 3H, CH_3), 3.21 (s, 3H Ar-CH_3), 4.55 (s, 2H, NH_2), 7.23-7.25 (dd, 2H, Ar-H, *J* = 7.5 Hz), 8.00-8.14 (dd, 2H, Ar-H, *J* = 8.0 Hz), 8.00 (s, 1H, C_5 CH), 9.11 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.12, 150.40, 145.11, 140.44, 125.40, 120.99, 119.40, 115.00, 100.20, 21.33, 12.30. MS (EI, *m/z* (%)): 286 (M^+). Anal. calcd. for $C_{14}H_{14}N_4OS$: C, 58.72; H 4.93; N, 19.57. Found: C, 58.70; H, 4.95; N, 19.55%.

6-(4-Methoxyphenyl)-3-methylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6e**): Color: Pale yellow. Yield: 70%. M.p.: 90-92 °C. FT-IR (KBr, ν, cm^{-1}): 3250 (NH_2), 3300 (NH), 1669 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H, CH_3), 3.22 (s, 3H, OCH_3), 4.44 (s, 2H, NH_2), 7.55-7.57 (dd, 2H, Ar-H, *J* = 7.0 Hz), 8.22-8.25 (dd, 2H, Ar-H, *J* = 7.5 Hz), 8.60 (s, 1H, C_5 CH), 9.01 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.10, 160.44, 150.12, 145.40, 135.42, 130.99, 120.40, 115.00, 102.20, 30.50, 20.30. MS (EI, *m/z* (%)): 302 (M^+). Anal. calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.60; H, 4.64; N, 18.50%.

3-Methyl-6-(4-nitrophenyl)imidazo[2, 1-b]thiazole-2-carbohydrazide (**6f**): Color: Yellow. Yield: 90%. M.p.: 130-132 °C. FT-IR (KBr, ν, cm^{-1}): 3340 (NH_2), 3325 (NH), 1669 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.10 (s, 3H, CH_3), 4.50 (s, 2H, NH_2), 7.99-8.00 (dd, 2H, Ar-H, *J* = 7.5 Hz), 8.22-8.25 (dd, 2H, Ar-H, *J* = 8.0 Hz), 8.62 (s, 1H, C_5 CH), 11.00 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.10, 155.44, 145.12, 140.41, 130.40, 125.90, 120.33, 110.22, 100.20, 12.33. MS (EI, *m/z* (%)): 317 (M^+). Anal. calcd. for $C_{13}H_{11}N_5O_3S$: C, 49.21; H, 3.49; N, 22.07. Found: C, 49.20; H, 3.50; N, 22.00%.

3-Methyl-6-(3-nitrophenyl)imidazo[2, 1-b]thiazole-2-carbohydrazide (**6g**): Color: Yellow. Yield: 85%.M.p.: 125-127 °C. FT-IR (KBr, ν, cm^{-1}): 3324 (NH_2), 3239 (NH), 1670 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.10 (s, 3H, CH_3), 4.43 (s, 2H, NH_2), 7.55-7.57 (m, 4H, Ar-H, *J* = 7.0 Hz), 8.01 (s, 1H, C_5 CH), 10.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.11, 155.30, 145.10, 140.40, 130.39, 125.80, 120.10, 110.23, 100.19, 12.22. MS (EI, *m/z* (%)): 317 (M^+). Anal. calcd. for $C_{13}H_{11}N_5O_3S$: C, 49.21; H 3.49; N, 22.07. Found: C,49.20; H, 3.47; N, 22.11%.

3-Methyl-6-phenylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6h**): Color: Brown. Yield: 70%. M.p.: 109-112 °C. FT-IR (KBr, ν, cm^{-1}): 3100 (NH_2), 3010 (NH), 1670 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.90 (s, 3H, CH_3), 4.45 (s, 2H, NH_2), 7.94-7.96 (m, 5H, Ar-H, *J* = 7.5 Hz), 8.52 (s, 1H, C_5 CH), 8.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.02, 145.50, 144.70, 130.50, 131.80, 125.90, 123.41, 120.39, 107.26, 11.91. MS (EI, *m/z* (%)): 273 (M^+). Anal. calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.30; H, 4.43; N, 20.59%.

6-(3-Bromophenyl)-3-methylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6i**): Color: Pale yellow. Yield: 80%. M.p.: 122-124 °C. FT-IR (KBr, ν, cm^{-1}): 3100 (NH_2), 3010 (NH), 1675 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.90 (s, 3H, CH_3), 4.48 (s, 2H, NH_2), 7.00-7.12 (m, 4H, Ar-H, *J* = 7.2 Hz), 7.55 (s 1H, C_5 CH), 8.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.11 145.55, 143.70, 133.50, 131.88, 130.96, 126.40, 123.30, 107.26, 12.90. MS (EI, *m/z* (%)): 351 (M^+). Anal. calcd. for$C_{13}H_{11}BrN_4OS$: C, 44.46; H, 3.16; N, 15.95. Found: C, 44.49; H, 3.19; N, 15.91%.

6-(3-Chlorophenyl)-3-methylimidazo[2, 1-b]thiazole-2-carbohydrazide (**6j**): Color: Pale yellow.Yield: 85%. M.p.: 116-118 °C. FT-IR (KBr, ν, cm^{-1}): 3110 (NH_2), 3100 (NH), 1670 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.01 (s, 3H, CH_3), 4.44 (s, 2H, NH_2), 7.00-7.13 (m, 4H, Ar-H, *J* = 7.5 Hz), 8.00 (s 1H, C_5 CH), 8.9 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.00, 145.50, 140.71, 132.50, 131.80, 130.90, 128.42, 126.33, 108.28, 12.95. MS (EI, *m/z* (%)):306 (M^+). Anal. calcd. for$C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; N, 18.26. Found: C, 50.93; H, 3.60; N, 18.29%.

3. Result and discussion

Considering the shortcomings of the conventional refluxing method like prolonged reaction time, resulting sometime in poor yield, moreover the formed product is associated with unreacted starting material.

Table 1. Optimization of the reaction condition for synthesis of compound **6i**.

Entry	Catalyst	Time (min)	Temp. (°C)	Yield (%)
1	Et_3N	4	110	40
2	$NaOCH_3$	6	120	20
3	KOH	6	110	30
4	NaOH	7	122	22
5	-	4	100	80

Table 2. Synthesis of 6-(4-substituted-phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide.

Entry	Products	Time (min)		Yield (%) [a]		Melting point (°C)
		Microwave heating	Conventional heating	Microwave heating	Conventional heating	
1	6a	5	360	80	85	110-112
2	6b	4	400	83	75	105-107
3	6c	5	370	75	70	111-113
4	6d	7	480	77	70	100-102
5	6e	4	500	70	65	90-92
6	6f	4	371	90	89	130-132
7	6g	5	360	85	85	125-127
8	6h	4	400	70	69	109-112
9	6i	4	350	80	80	122-124
10	6j	5	360	85	83	116-118

[a] Isolated yields.

The newly adapted microwave approach is observes to shorten the reaction time significantly, with efficient utilization of starting material. The studied method for synthesis is incorporated with good yield without use of costly catalyst, or solvent. Synthesis of starting material ethyl 2-amino-4-methylthiazole-5-carboxylate is carried out by known method [45] as shown in Scheme 1.

Equimolar quantity of ethyl 2-amino-4-methylthiazole-5-carboxylate (**3**), substituted phenacyl bromide (**4**) and hydrazinehydrate (**5**) were added sequentially in same pot, irradiated with microwave irradiation to give desired product substituted-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide (**6a-j**). The formed product was characterized with the help of spectral data IR, ^{1}H NMR, ^{13}C NMR and Mass. The reaction is shown in Scheme 2.

FT-IR spectra of the compound clearly reveals the presence of sharp amidic carbonyl stretching vibration frequency observed at 1670 cm^{-1}, with NH and NH_2 broad stretching vibration and at 3330 and 3247 cm^{-1}, respectively. ^{1}H NMR clearly showing the presence of one sharp singlet for CH_3 at δ 2.69 ppm, singlet at δ 4.55 ppm for NH_2 protons, singlet at δ 8.33 ppm for CH protons, and singlet at δ 9.61 ppm for NH, and all remaining protons are in their corresponding aromatic region at δ 7.41 to 7.87 ppm. In mass spectrum compound **6b** shows peak at 307 due to [M+1]. The plausible mechanism is shown in Scheme 3.

Mechanism of the reaction indicates the propagation of reaction takes place through nucleophilic attack of cyclic nitrogen on substituted phenacyl bromide, followed by cyclization to form five membered imidazothiazole carboxylate rings. Lastly hydrazine hydrates reacts with ester to form the final product.

Discrete reaction conditions are explored for the optimization of reaction including temperature, catalyst and time. Reaction carried out at room temperature without use of solvent and catalyst doesn't get completed even after 3 hours of irradiation of microwave radiation. Uses of various catalysts are shown to alter the yield of the product as well as time for completion of reaction. When there was use of strong base or strong acid as catalyst the yield of product appeared was poor, time required for completion of reaction was also more [46]. Use of mild base or mild acid as a catalyst shows further increase in the product yield with lesser time, up to some extent. The best yield in less time is observed when the reaction is carried out without catalyst under microwave condition [47]. The temperature for the reaction is observed to be 100 to 120 °C without solvent. All the three observed optimized reaction condition shows that, the reaction is completed with excellent yield in less time when it is carried out under solvent and catalyst free condition with temperature 100 to 120 °C in microwave. The results of the optimization are described in Table 1.

With these results of optimization of the reaction, we tried various substituted phenacyl bromide for inspecting the scope and capability of reaction. Method of the reaction is observed to applicable for various derivatives, with good to excellent yield. It was observed that position and nature of the substituent on the phenyl ring of substituted phenacyl bromide dose not strongly affect the reaction, however there was mild effect observed that electron withdrawing groups on substituted phenacyl bromide were responsible for increase in the yield of the reaction, up to some extent while electron donate groups were decreasing the yield up to some extent. These results are described in Table 2.

In conclusion herein we have successfully report an easy, practical and efficient access for synthesis of new 6-(4-sub phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide by solvent and catalyst free one pot microwave assisted procedure. The protocol reveals significant advantages as avoiding use toxic solvents and catalyst, easy isolation of product, high yield, and atom economy, mild and simple condition with shorter reaction time. This process provides cheap and eco-friendly method for synthesis of new 6-(4-sub phenyl)-3-methylimidazo[2,1-*b*]thiazole-2-carbohydrazide derivatives.

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