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Synthesis One Pot of imidazo[2,1-*b*]thiazole via Groebke-Blackburn-Bienaymé Reaction under Free Catalyts †

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Abstract: The imidazo[2,1-*b*]thiazole scaffold is widely present in natural and synthetic compounds with important properties or biological activities such as anti-inflammatory, antibacterial, antituberculosis, cytotoxic, anthelmintic, antihypertensive or herbicidal. The isocyanide multicomponent reaction (I-MCR) process is a greener alternative efficient synthetic tool. Herein we described a novel methodology one pot to the synthesis of imidazo[2,1-*b*]thiazole by Groebke-Blackburn-Bienaymé reaction (GBBR) using a few explored 3-formylchromone.

Keywords: imidazo[2,1-b]thiazole; I-MCR; Groebke-Blackburn-Bienaymé reaction

1. Introduction

Imidazo[2,1-*b*]thiazole is the framework of many natural and synthetic products, the fused five-membered heterocyclic rings containing bridgehead nitrogen and a sulfur atom are the core of molecules exhibiting important biological activities such as anthelmintic, antialzheimer, antihypertensive and herbicidal (Figure 1) [1–4].

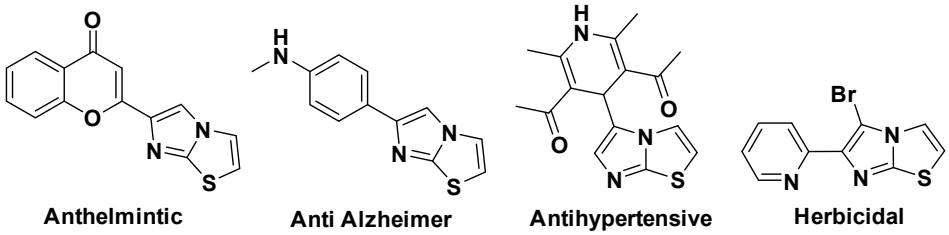

Figure 1. Imidazo[2,1-*b*]thiazole present in bioactive molecules.

As the imidazo[2,1-*b*]thiazole scaffolds had significant applications, a large number of routes for their synthesis have been developed. However, the classical methods imply stepwise resulting in long time reactions, high temperatures, limited scope, low yields, metal-catalyzed [5–7].

The isocyanide based multicomponent reactions (I-MCR) have been used as an alternative to overcome this problem. The Groebke-Blackburn-Bienaymé reaction (GBBR) provides simplicity in one pot reaction and high atom economy. However, there are few reports of GBBR towards imidazo[2,1-b]thiazoles compared with imidazo[1,2-*a*]pyridines [8].

As far as literature survey concern, few reports of synthesis of imidazo[2,1-*b*]thiazoles by I-MCR process have been reported (Scheme 1) [9].

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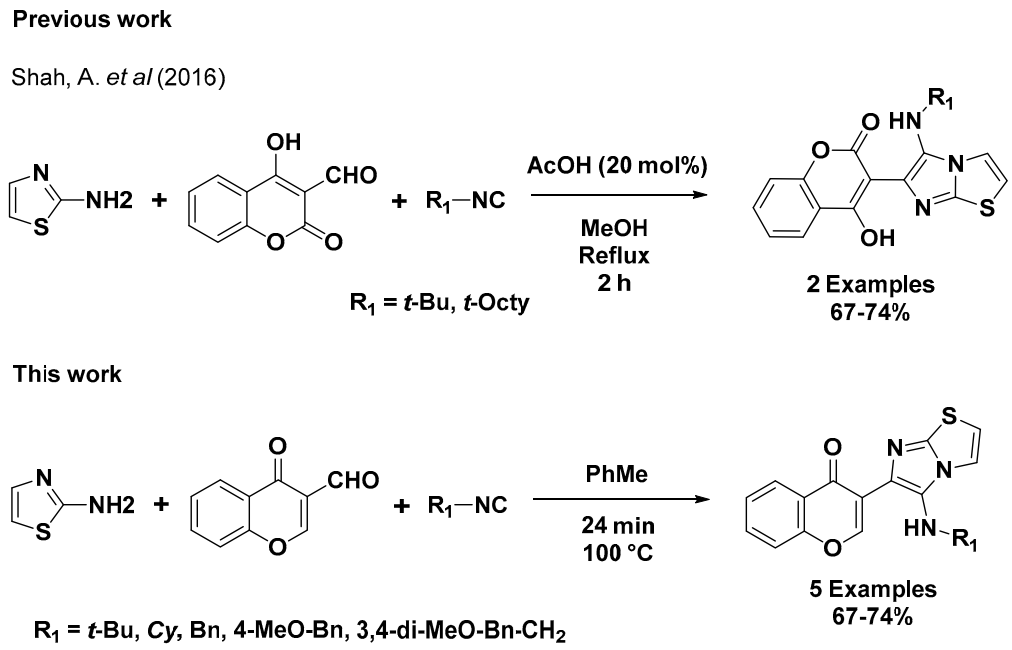


Scheme 1. Previous reports of synthesis of Imidazo[2,1-*b*]thiazole.

Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activities [10]. Herein we report the synthesis of imidazo[2,1-*b*]thiazoles holding chromone moiety by GBBR increasing the diversity of isocyanides.

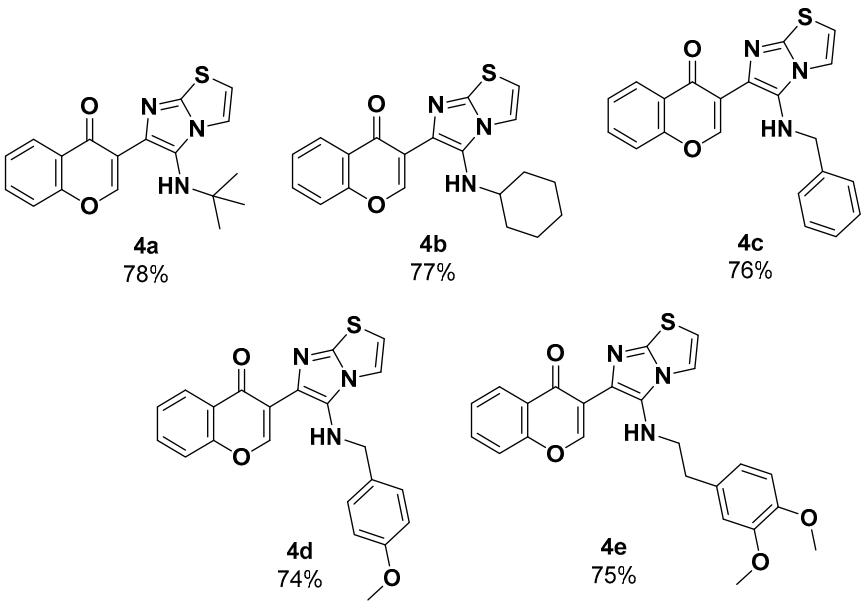
2. Results and Discussion

The optimization of reaction was conducted by 3-formylchromone (**1**), 2-aminothiazole (**2**) and *tert*-butyl isocyanide (**3**), initially the GBBR was performed stirring in methanol at 85 °C without catalyst (Table 1, entry 1) giving the desired product in 33% of yield, to perform the reaction acetonitrile was chosen but similar yield was obtained (entry 2), then reaction was carry out employing toluene affording the product in 68% of yield (entry 3), finally carrying out the reaction in the same conditions with toluene with increase temperature to 100 °C improve the yield to 78% and the reaction time decreased to 30 min (entry 4).

Table 1. Screening conditions for the synthesis of **4a.**

Entry	Solvent	Time (min)	Temp °C	Yield
1	MeOH	60	85	33
2	MeCN	60	85	40
3	PhMe	60	85	68
4	PhMe	30	100	78

After optimizing the conditions, we explored the versatility of the methodology by variations of isocyanide reagents. The respective imidazo[2,1-*b*]thiazoles products **4a–e** (Scheme 2) were obtained in moderated yields (74–78%), synthesized under the optimized conditions (Table 1, entry 4).



Scheme 2. Sustrate scope.

3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometers (500 MHz) The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm), Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using the Mestre Nova software (version 6.0.2-5475). IR spectra were recorded on a Perkin Elmer 100 spectrometer by the ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max}/cm^{-1}). FT-IR spectra were analyzed using the Report Builder software (Rev. 2.01). HRMS spectra were acquired on a Maxis-Impact ESI(+)-QqTOF Bruker mass spectrometer. HRMS spectra were analyzed using the data Analysis (Bruker, version 4.1). Microwave assisted reactions were performed in closed vessel mode using a monomodal CEM Discover unit. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexanes with AcOEt (7:3; *v*/*v*) as mobile phase. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Commercially available starting materials were used without further purification. The solvents were distilled and dried according standard procedures. Commercially available reagents were purchased in Sigma-Aldrich and were used without further purification. Structure names and drawings were performed using the ChemBioDraw Ultra software (version 13.0.0.3015).

3.2. General Procedure (GP)

In a flask with a magnetic stirring bar, to a 0.5 M solution of aldehyde (1.0 equiv.) in anhydrous toluene [0.5 M], amine (1.0 equiv.) and isocyanide (1.0 equiv.) were added sequentially and the reaction mixture was heated (100 °C) for 30 min. Then, the solvent was removed until dryness and the crude was immediately purified by silica-gel column chromatography using a mixture of hexanes with ethyl acetate (7/3; *v*/*v*) to afford the corresponding products **4a**–**4e**.

3.3. Spectral Data

3.3.1. Synthesis and Characterization of the 3-(5-(tert-butylamino)imidazo [2,1-b] thiazol-6-yl)-4H-chromen-4-one (**4a**)

According to the GP, 3-formylchromone (44.8 mg, 1 mmol), 2-aminothiazole (25.8 mg, 1 mmol) and tert-butyl isocyanide (27.9 μL, 1 mmol) were reacted together in anhydrous toluene (0.5 mL) to afford the product **4a** (66 mg, 78%) as orange solid; mp = 228 °C; R_f = 0.38 (Hexanes-AcOEt = 7/3; *v*/*v*). ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.66 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.73–7.69 (m, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 4.5 Hz, 1H), 4.90 (s, 1H), 1.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 176.0, 156.0, 155.6, 145.6, 133.6, 130.4, 130.3, 126.4, 125.3, 124.2, 121.4, 118.3, 118.2, 111.1, 55.6, 29.7; FT-IR (ATR) ν_{max}/cm^{-1} 3286 (N-H), 1629 (C=O); HRMS (ESI$^+$): *m*/*z* calcd. for $C_{18}H_{18}N_3O_2S^+$ 340.1114, found 340.1118.

3.3.2. Synthesis and Characterization of the 3-(5-(cyclohexylamino)imidazo[2,1-b] thiazol-6-yl)-4H-chromen-4-one (**4b**)

According to the GP, 3-formylchromone (44.8 mg, 1 mmol), 2-aminothiazole (25.8 mg, 1 mmol) and cyclohexyl isocyanide (31.7 μL, 1.0 mmol) were reacted together in anhydrous toluene (0.5 mL) to afford the product **4b** (70 mg, 77%) as brown solid; mp = 170 °C; R_f = 0.31 (Hexanes-AcOEt = 7/3; *v*/*v*). ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.70 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.47–7.43 (m, 1H), 7.38 (d, J = 4.5 Hz, 1H), 6.74 (d, J = 4.5 Hz, 1H), 2.76–2.69 (m, 1H), 1.87–1.80 (m, 2H), 1.70–1.64 (m, 2H), 1.55–1.50 (m, 1H), 1.18–1.07 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 176.2, 156.1, 155.3, 144.9, 133.7, 132.1, 126.8, 126.5, 125.3, 124.3, 121.0, 118.3, 117.5, 111.6, 57.8, 34.1, 25.8, 25.2; FT-IR (ATR) ν_{max}/cm^{-1} 3291 (N-H), 1638 (C-O); HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{20}N_3O_2S^+$ 366.1270, found 366.1271.

3.3.3. Synthesis and Characterization of the 3-(5-(benzylamino)imidazo[2,1-b]thiazol-6-yl)-4H-chromen-4-one (**4c**)

According to the GP, 3-formylchromone (44.8 mg, 1 mmol), 2-aminothiazole (25.8 mg, 1.0 mmol) and benzyl isocyanide (31.1 μL, 1.0 mmol) were reacted together in anhydrous toluene (0.5 mL) to afford the product **4c** (71 mg, 76%) as orange solid; mp = 124 °C; R_f = 0.32 (Hexanes-AcOEt = 1/3; *v*/*v*). ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.45 (s, 1H), 8.27 (dd, J = 8.0, 1.4 Hz, 1H), 7.71–7.67 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.45–7.41 (m, 1H), 7.27–7.25 (m, 1H), 7.13–7.10 (m, 2H), 7.09–7.06 (m, 3H), 6.71 (d, J = 4.5 Hz, 1H), 5.69 (s, 1H), 4.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 176.3, 156.0, 155.1, 139.5, 133.6, 132.2, 128.5, 128.4, 127.2, 126.4, 125.3, 124.2, 118.2, 117.3, 111.8, 53.6; FT-IR (ATR) ν_{max}/cm^{-1} 3282 (N-H), 1631(C-O); HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{16}N_3O_2S^+$ 374.0957, found 374.0963.

3.3.4. Synthesis and Characterization of the 3-(5-((4-methoxybenzyl)amino)imidazo [2,1-b]thiazol-6-yl)-4H-chromen-4-one (**4d**)

According to the GP, 3-formylchromone (44.8 mg, 1.0 mmol), 2-aminothiazole (25.8 mg, 1.0 mmol) and 4-methoxybenzyl isocyanide (37.5 mg, 1.0 mmol) were reacted together in anhydrous toluene (1.0 mL) to afford the product **4d** (74 mg, 74%) as pale yellow oil; R_f = 0.11 (Hexanes-AcOEt = 7/3; *v*/*v*). ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.42 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.71–7.67 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.46–7.42 (m, 1H), 7.30 (d, J = 3.9 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 3.8 Hz, 1H),6.54 (d, J = 7.8 Hz, 2H), 5.51 (s, 1H), 3.97 (s, 2H), 3.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 176.1, 158.9, 155.9, 155.1, 133.6, 132.0, 131.6, 129.9, 129.0, 127.4, 126.4, 125.3, 124.2, 118.2, 117.3, 114.3, 113.7, 111.8, 55.2, 53.1; FT-IR (ATR) ν_{max}/cm^{-1} 3282 (N-H), 1638 (C=O); HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{18}N_3O_3S^+$ 404.1063, found 404.1083.

3.3.5. Synthesis and Characterization of the 3-(5-((3,4-dimethoxyphenethyl)amino) imidazo[2,1-b]thiazol-6-yl)-4H-chromen-4-one (**4e**)

According to the GP, 3-formylchromone (44.8 mg, 1.0 mmol), 2-aminothiazole (25.8 mg, 1.0 mmol) and 3,4-dimethoxyphenethyl isocyanide (50 mg, 1.0 mmol) were reacted together in anhydrous toluene (1.0 mL) to afford the product **4e** (84 mg, 75%) as pale brown solid; mp = 152.8 °C; R_f = 0.30 (Hexanes-AcOEt = 7/3; *v*/*v*). ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.65 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.74–7.69 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.47–7.43 (m, 1H), 7.27 (s, 1H), 7.25–7.22 (m, 1H), 6.77–6.75 (m, 1H), 6.70–6.66 (m, 2H), 4.12 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.28–3.24 (m, 2H), 2.74–2.70 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 176.0, 155.9, 155.0, 148.8, 147.4, 144.8, 133.6, 132.6, 131.7, 126.3, 125.2, 123.9, 120.6, 120.2, 118.1, 117.1, 112.1, 112.0, 111.1, 55.8, 50.0, 36.1; FT-IR (ATR) ν_{max}/cm^{-1} 3319 (N-H), 1608 (C-O); HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{22}N_3O_4S^+$ 448.1325, found 448.1315.

4. Conclusions

This work is a contribution of the synthesis of bis-heterocycles containing the imidazo[2,1-*b*] thiazole framework bound with chromone via a GBBR with classical conditions under free catalyst. The synthesized products may have interesting applications, because they contain heterocyclic frameworks such as chromone present in numerous compounds exhibiting biological properties.

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