chemistry proceedings

MDPI

Proceeding Paper

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

David Calderón-Rangel, Karla A. González Pérez, Alejandro Corona Díaz and Rocío Gámez-Montaño *

Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato CP 36050, México; david.calderon@ugto.mx (D.C.-R.); ka.gonzalezperez@ugto.mx (K.A.G.P.); alejandro.corona@ugto.mx (A.C.D.)

* Correspondence: rociogm@ugto.mx; Tel.: +52-473-73-20-006 (ext. 8191)

† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

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, anti-bacterial, anti-tuberculosis, cytotoxic, anthelmintic, anti-hypertensive, or herbicidal properties. The isocyanide multicomponent reaction (I-MCR) process is a greener alternative and efficient synthetic tool. Herein, we describe a novel methodology, one-pot synthesis for the synthesis of imidazo[2,1-*b*]thiazole by Groebke–Blackburn–Bienaymé reaction (GBBR) using little-explored 3-formylchromone.

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

1. Introduction

Many natural and synthetic products are based on the imidazo[2,1-*b*]thiazole framework. 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, anti-alzheimer, anti-hypertensive, and herbicidal properties (Figure 1) [1–4].

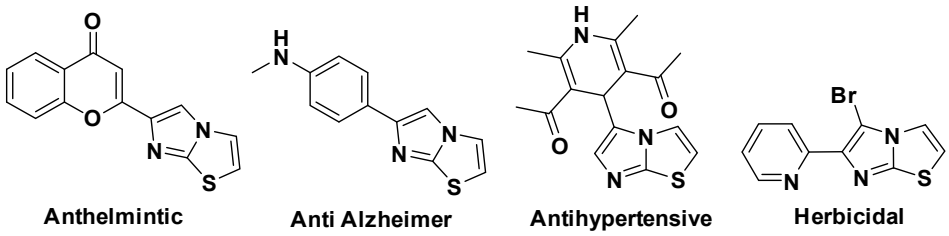


Figure 1. Imidazo[2,1-*b*]thiazole present in bioactive molecules.

As the imidazo[2,1-*b*]thiazole scaffolds have significant applications, a large number of routes for their synthesis have been developed. However, the classical methods imply stepwise synthesis, resulting in long time reactions, high temperatures, limited scope, low yields, and metal-catalyzed processes [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 a one-pot reaction and high atom economy. However, there are few reports of GBBR regarding imidazo[2,1-*b*]thiazoles compared with imidazo[1,2-*a*]pyridines [8].

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

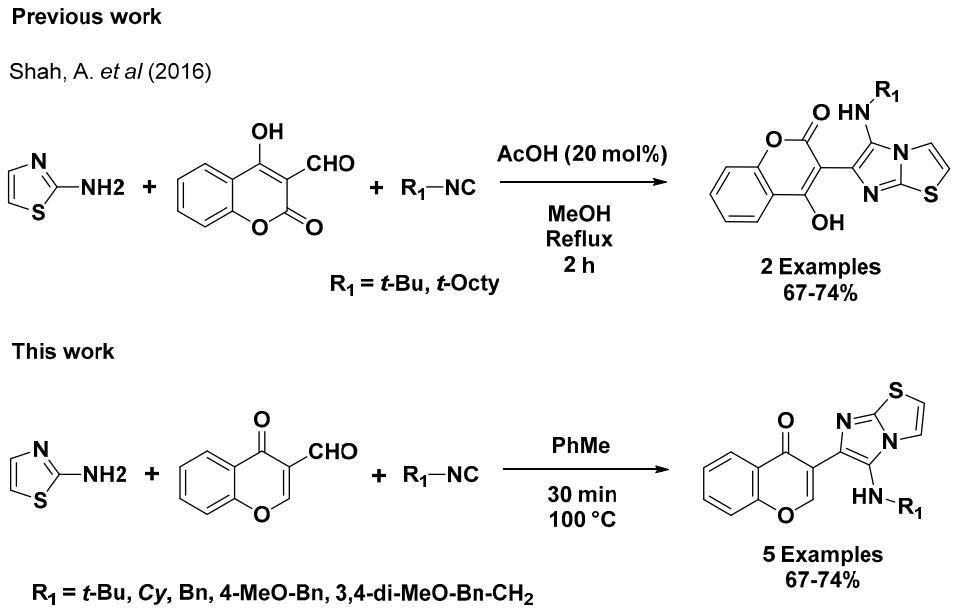
Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activities [10]. Herein, we report the synthesis of imidazo[2,1-*b*]thiazoles holding chromone moiety by GBBR, increasing the diversity of isocyanides.

check for updates

Citation: Calderón-Rangel, D.; Pérez, K.A.G.; Díaz, A.C.; Gámez-Montaño, R. One-Pot Synthesis of Imidazo [2,1-*b*]thiazole via Groebke–Blackburn–Bienaymé Reaction under Free Catalyts. *Chem. Proc.* **2023**, *14*, 103. https://doi.org/10.3390/ecsoc-27-16095

Academic Editor: Julio A. Seijas

Published: 15 November 2023



Scheme 1. Previous reports of synthesis of imidazo[2,1-*b*]thiazole [9].

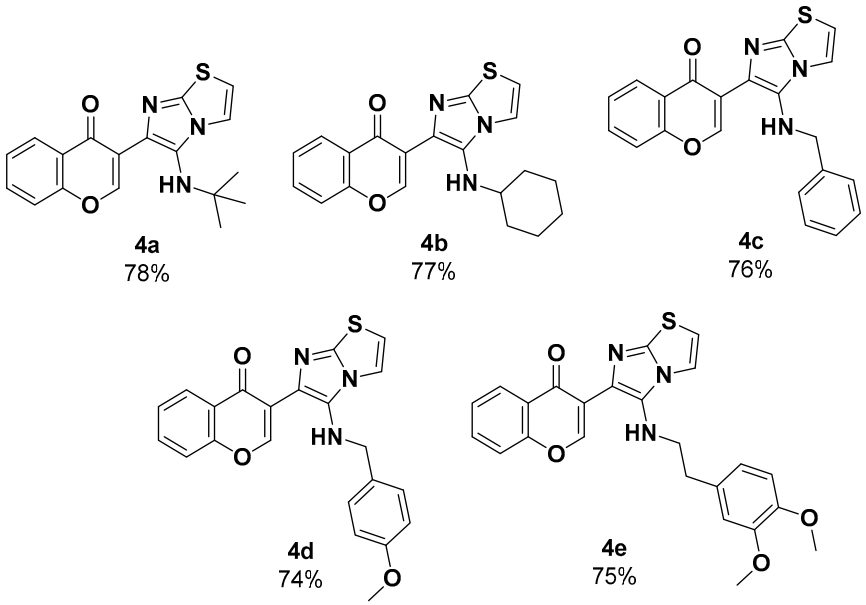
2. Results and Discussion

The optimization of the reactions was conducted by 3-formylchromone (**1**), 2-aminothiazole (**2**), and *tert*-butyl isocyanide (**3**). Initially, the GBBR was performed by stirring in methanol at 85 °C without a catalyst (Table 1, entry 1), giving the desired product at a 33% yield. To perform the reaction again acetonitrile was chosen, but a similar yield was obtained (entry 2); then, the reaction was carried out by employing toluene, affording the product in 68% of yield (entry 3). Finally, carrying out the reaction in the same conditions with toluene and with an increase in temperature to 100 °C improved the yield to 78% and decreased the reaction time 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 through variations of isocyanide reagents. The respective imidazo[2,1-*b*]thiazoles products **4a**–**e** (Scheme 2) were obtained in moderate yields (74–78%), synthesized under the optimized conditions (Table 1, entry 4).



Scheme 2. Substrate 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 $CDCl_3$ was used for NMR samples. Chemical shifts are reported in parts per million (δ/ppm). The internal reference for NMR spectra was 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 (PerkinElmer Inc. Waltham, MA, USA) by using the ATR method employing neat compounds. The wavelengths are reported in reciprocal centimeters ($_{Vmax}/cm^{-1}$). FT-IR spectra were analyzed using the Report Builder software (Rev. 2.01). HRMS spectra were acquired using a Maxis-Impact ESI(+)-QqTOF Bruker mass spectrometer (Bruker, Billerica, MA, USA). HRMS spectra were analyzed using the data analysis software (Bruker, version 4.1). Microwave-assisted reactions were performed in closed-vessel mode using a monomodal CEM Discover unit (CEM Corporation, Matthews, NC, USA). 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 the mobile phase. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Commercially available starting materials were used without further purification. The solvents were distilled and dried according to standard procedures. Commercially available reagents were purchased from 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, amine (1.0 equiv.) and isocyanide (1.0 equiv.) were added sequentially to a 0.5 M solution of aldehyde (1.0 equiv.) in anhydrous toluene [0.5 M], and the reaction mixture was heated (100 °C) for 30 min. Then, the solvent was removed to the point of dryness and the crude was immediately purified by using silica gel column chromatography employing 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)-4*H*-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) $_{Vmax}$/cm^{-1} 3286 (N-H), 1629 (C=O); HRMS (ESI$^+$): *m*/*z* calcd. for $C_{18}H_{18}N_3O_2S^+$ 340.1114, found to be 340.1118.

3.3.2. Synthesis and Characterization of the 3-(5-(Cyclohexylamino)imidazo[2,1-*b*] thiazol-6-yl)-4*H*-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) $_{Vmax}$/cm^{-1} 3291 (N-H), 1638 (C-O); HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{20}N_3O_2S^+$ 366.1270, found to be 366.1271.

3.3.3. Synthesis and Characterization of the 3-(5-(Benzylamino)imidazo[2,1-*b*] thiazol-6-yl)-4*H*-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) $_{Vmax}$/cm^{-1} 3282 (N-H), 1631(C-O); HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{16}N_3O_2S^+$ 374.0957, found to be 374.0963.

3.3.4. Synthesis and Characterization of the 3-(5-((4-Methoxybenzyl)amino)imidazo[2,1-*b*] thiazol-6-yl)-4*H*-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) $_{Vmax}$/cm^{-1} 3282 (N-H), 1638 (C=O); HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{18}N_3O_3S^+$ 404.1063, found to be 404.1083.

3.3.5. Synthesis and Characterization of the 3-(5-((3,4-Dimethoxyphenethyl)amino)imidazo 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 to be 448.1315.

4. Conclusions

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

Author Contributions: Editing, writing, D.C.-R.; validation, K.A.G.P.; synthetic investigation, methodology, A.C.D.; supervision, methodology, writing review and editing, funding acquisition, R.G.-M. All authors have read and agreed to the published version of the manuscript.

Funding: R.G.-M. thanks CONACYT for financial support through the CONACYT CB-2016-285622. and DAIP-UG, 005/2022 projects. D.C.R. (666925/2782364) and A.C.D. (490344/2907767) thank CONACYT-México for a scholarship and Laboratorio Nacional de Caracterizacion de Propiedades Fisicoquímicas y Estructura Molecular (CONACYT-México, Project: 123732).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Hamid, A.; Philippe, R.L.; Catarina, B.; Raymond, C.; Marc, P.; Philippe, M.L.; Christian, B.; Gayral, P. Imidazo[2,1-*b*]thiazoles: Analogues du lévamisole. *Eur. J. Med. Chem.* **1987**, *22*, 463.
2. Yousefi, B.H.; Manook, M.; Drzezga, A.; Reutern, B.V.; Schwaiger, M.; Wester, H.J.; Henriksen, G. Synthesis and evaluation of ^{11}C-labeled imidazo[2,1-*b*]benzothiazoles (IBTs) as PET tracers for imaging *β*-amyloid plaques in Alzheimer's disease. *J. Med. Chem.* **2011**, *54*, 949. [CrossRef] [PubMed]
3. Budriesi, R.; Loan, P.; Locatelli, A.; Cosconati, S.; Leoni, A.; Ugenti, M.P.; Andreani, A.; Toro, R.D.; Bedini, A.; Spampinato, S.; et al. Imidazo[2,1-*b*]thiazole system: A scaffold endowing dihydropyridines with selective cardiodepressant activity. *J. Med. Chem.* **2008**, *51*, 1592. [CrossRef] [PubMed]
4. Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Andreani, F.; Gehret, J.-C. Synthesis of imidazo[2,1-*b*]thiazoles as herbicides. *Pharm. Acta Helv.* **1996**, *71*, 247. [CrossRef]
5. Cesurl, Z.; Gunerl, H.; Otuk, G. Synthesis and antimycobacterial activity of new imidazo[2,1-*b*]thiazole derivatives. *Eur. J. Med. Chem.* **1994**, *29*, 981. [CrossRef]
6. Bakherad, M.; Keivanloo, A.; Bahramian, B.; Kamali, T.A. Synthesis of novel 6-(substituted benzyl) imidazo[2,1-*b*][1,3]thiazole catalyzed by polystyrene-supported palladium (ii) ethylenediamine complex. *J. Braz. Chem. Soc.* **2009**, *20*, 907. [CrossRef]
7. Dzhavakhishvili, S.G.; Borisov, A.V.; Nikitchenko, V.M.; Kovalenko, S.N. Features of the reaction of unsymmetrical 2-mercapto-imidazoles with aromatic and aliphatic ketones. *Chem. Heterocycl. Compd.* **2007**, *43*, 98–105. [CrossRef]
8. Boltjes, A.; Dömling, A. The Groebke-Blackburn-Bienaymé Reaction. *Eur. J. Org. Chem.* **2019**, *42*, 7007–7049. [CrossRef] [PubMed]

9. Manvar, P.; Shaikh, F.; Kakadiya, R.; Mchariya, K.; Khunt, R.; Pandey, B.; Shah, A. Synthesis of novel imidazo[1,2-*a*]pyridine-4-hydroxy-2*H*-coumarins by Groebke–Blackburn–Bienaymé multicomponent reaction as potential NS5B inhibitors. *Tetrahedron* **2016**, *72*, 1293. [CrossRef]
10. Keri, R.S.; Budagumpi, S.; Pai, R.K.; Balakrishna, R.G. Chromones as a privileged scaffold in drug discovery: A review. *Eur. J. Med. Chem.* **2014**, *78*, 340–374. [CrossRef] [PubMed]