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An Efficient Synthesis of 2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-Carboxylic Acid

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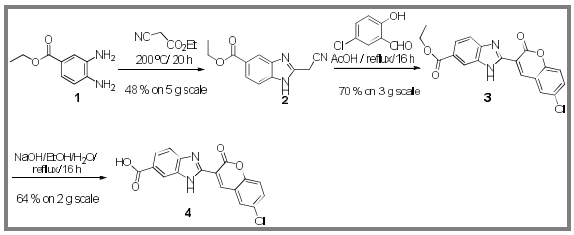
ABSTRACT

A fast and efficient protocol have explored to access the various benzimidazole constituted chromenes from commercially available Ethyl-3,4-diaminobenzoate. After subsequent transformation the benzimidazole constituted cyanoacetic acid has been produced this was confirmed by spectral analysis.

Graphical Abstract



Synthesis of imidazole derivative

Keywords: Ethyl cyanoacetate, Chromenes, Imidazole, chlorosalicylaldehyde, Spectral analysis,

INTRODUCTION

Benzimidazole and its derivatives have been displayed promising activity in the treatment of several diseases, drawing much attention as important pharmacophore and privileged structure in medicinal chemistry. Benzimidazoles have been found to be effective against various strains of microorganisms based on their biochemical and pharmacological studies as chemotherapeutic agents. The nucleus possesses structural similarity with purine and has been used as biomimetics of guanine residues.

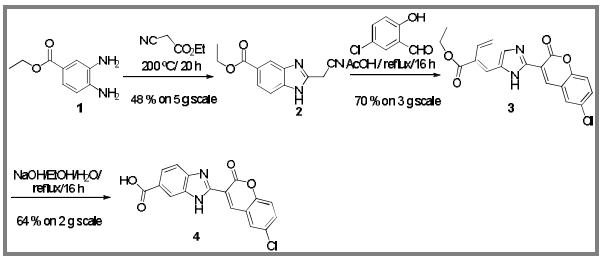
Benzimidazole fused or benzimidazoles constituted molecules have been a major source of new drugs to explore, and many successful drugs were originally synthesized to mimic the action of benzimidazole molecules found in nature [**1-9**]. The numerous benzimidazole embracing coumarin derivatives structural scaffolds containing compounds are highly diverse and often provide highly specific biological activities [**10-12**]. To this end the proposition that essentially all benzimidazole structural frameworks have some receptor binding capacity [**13**]. The benzimidazoles in combination with various quinazolines [**14**], chromen [15], and thiochromen [**16-20**] structures have attracted

considerable attention. These heterocyclic ring-systems due to their presence in many naturally and synthetically derived molecules, which possess a wide range of biological properties and frequently, hold promising pharmaceutical potential [21]. 4-amino3-benzimidazol-2-ylhydro quinolin-2-ones are a class of potent RTK inhibitors involved in important signal transduction pathways within the cell with attractive physicochemical and pharmacokinetic properties and significant efficacy in murine and human xenograft tumor models [22].

The renin–angiotensin system (RAS) [23] is known to play an important role in cardiovascular regulation [24] and the maintenance of blood pressure and electrolyte balance. AngiotensinII [25] (AngII) is active hormone of RAS and it mediates a variety of physiological functions through stimulation of specific receptors. There are at least two distinct receptor sub-types [26, 27] designed as AT1 and AT2. In view of their biological importance we herein report synthesis of 2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylic acid.

MATERIALS AND METHODS

Chemicals and solvents were reagent grade and used without further purification. The ^{1}H NMR spectra were recorded in the indicated solvent on a Varian 300 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 F_{254}).



Scheme 1. Synthesis of imidazole derivative

Ethyl 2-(cyanomethyl)-1H-benzo[d]imidazole-5-carboxylate (2): A mixture of Ethyl-3,4-diaminobenzoate (1) (0.01 mole) and ethyl cyanoacetate (0.01 mole) were heated to 200°C for 20 h. The reaction mixture was monitored by TLC. The mixture was allowed rt and the reaction mixture was poured into cold water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product. The crude compound was purified by column using 100-200 mesh silica and eluting with 15% Acetone in CH_2Cl_2 to afford Ethyl 2-(cyanomethyl)-1H-benzo[d]imidazole-5-carboxylate **(2).**

Ethyl-2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylate (3): To a solution of Ethyl 2-(cyanomethyl)-1H-benzo[d]imidazole-5-carboxylate **(2)** (0.01 mole) in glacial acetic acid (30 mL) was added 5-chlorosalicylaldehyde (0.01 mole) at rt and the reaction mixture was reflux for 16 h. The reaction mixture was allowed to cool to room temperature and filtered. The residue obtained was washed with diethyl ether and dried over vacuum to afford Ethyl-2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylate **(3)**.

2-(6-Chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylic acid (4): To a solution of Ethyl-2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylate **(3)** in EtOH was added NaOH in water and the reaction mixture was reflux for 16 h. Ethanol present in the reaction mixture was concentrated under reduced pressure and neutralized with acetic acid (pH=4). The precipitated solid was filtered and residue was co-distilled with benzene for 5 times and dried under vacuum to afford the 2-(6-Chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylic acid **(4)**.

RESULTS AND DISCUSSION

A mixture of Ethyl-3,4-diaminobenzoate **(1)** and ethyl cyanoacetate was reacted to afford 3 Ethyl 2-(cyanomethyl)-1H-benzo[d]imidazole-5-carboxylate **(2)**, which reacted with 5-chlorosalicylaldehyde in glacial acetic acid (30 mL) to afford Ethyl-2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylate **(3).** Further afford Ethyl-2-(6-chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylate treated with NaOH to form 2-(6-Chloro-2-oxo-2H-chromen-3-yl)-1H-benzo[d]imidazole-6-carboxylic acid **(4)**. All the synthesized compounds were characterized by spectral analyses.

The ^{1}H-NMR showed the signals at δ 10.01 (brs, 1H) for –NH group 8.41 (d, 1H), 8.02 (s, 1H), 7.62 (d, 1H), for aromatic 4.41 (q, 2H) and 4.20 (s, 2H) for 2 x –CH_2- and 1.40 (t, 3H) for -CH_3. The Mass spectrum showed peak at 230.1 $[M+H]^+$. This data confirms the structure of compound **2** and in the similar way the structures of compound **3** and **4** were confirmed. Compound **4** showed ^{1}H-NMR signals at δ 12.60 (brs, 1H) for carboxylic acid, 9.05 (s, 1H) for –NH group 8.20 (m, 2H), 7.85 (d, 1H), 7.75 (d, 1H), 7.60 (m, 3H) for aromatic group (Figures 1, 3 and 5). The mass spectrum showed signal at 341.0 $[M+H]^+$ The characterization data presented in table 1.

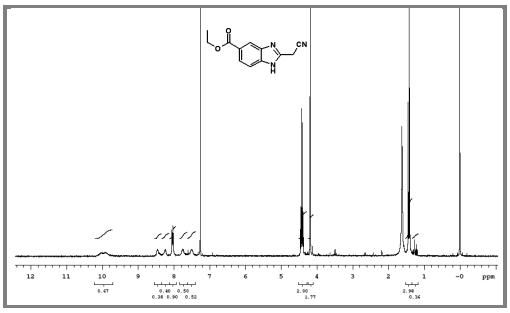


Figure 1. ^{1}H NMR Spectrum of compound **2**

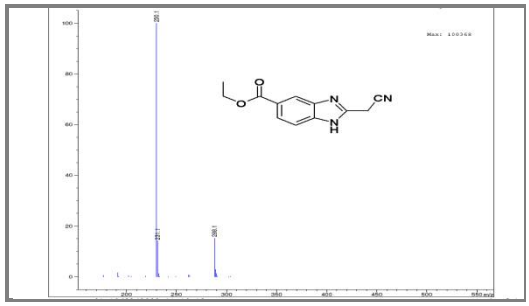


Figure 2. Mass Spectrum of compound **2**

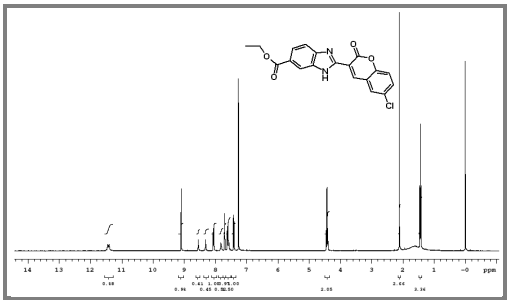


Figure 3. ^{1}H NMR Spectrum of compound **3**

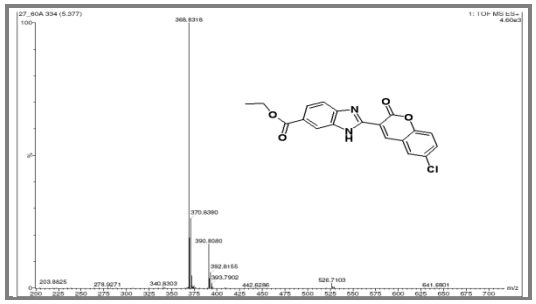


Figure 3. Mass Spectrum of compound **3**

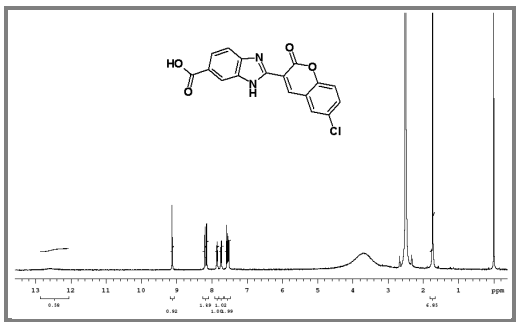


Figure 5. ^{1}H NMR Spectrum of compound **4**

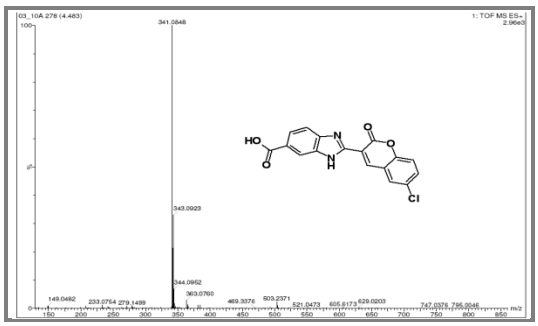


Figure 6. Mass Spectrum of compound **4.**

Table 1. Characterization of ^{1}**H NMR**

S.No	Compound	^{1}**H NMR** (400 MHz, DMSO-d_6)	**Mass**: *m/z* $[M+H]^+$	**Yield (%)**
1	2	10.01 (brs, 1H), 8.41 (d, 1H), 8.02 (s, 1H), 7.62 (d, 1H), 4.41 (q, 2H), 4.20 (s, 2H), 1.40 (t, 3H)	230.1	82
2	3	11.42 (brs, 1H), 9.02 (s, 1H), 8.42 (d, 1H), 8.05 (s, 1H), 7.80 (s, 1H), 7.64 (d, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 4.42 (q, 2H), 1.40 (t, 3H).	368.8	78
3	4	12.60 (brs, 1H), 9.05 (s, 1H), 8.20 (m, 2H), 7.85 (d, 1H), 7.75 (d, 1H), 7.60 (m, 3H). Mass	341.0	73

APPLICATION

Imidazoles and chromenes are an important class of heterocyclic compounds having important biological activities. Many of the methods reported for the synthesis of these compounds are associated with the use of hazardous organic solvents, long reaction time, use of toxic amine-based catalysts, and lack of general applicability. Thus, the development of an inexpensive, mild, general, environmentally and commercially available catalyst for synthesis of these compounds remains an issue of interest.

CONCLUSION

In the present communication, attempt has been made to present the synthetic strategies and of Imidazoles. Synthetic procedure and characterization of title compounds were critically discussed.

REFERENCES

1. R. C. Elderfield, Heterocyclic Compounds: Six-membered heterocycles containing two hetero atoms and their benzo derivatives, *John Wiley*, **1957**.
2. W. Lwowski, A. R. Katritzky, Comprehensive heterocyclic chemistry: the structure, reactions, synthesis and uses of heterocyclic compounds, *Med Chem*, **1987**, 8, 234-241.
3. A. A.Spasov, I. N. Yozhitsa, I. L. Bugaeva, V. A. Anisimova, Benzimidazole derivatives: spectrum of pharmacological activity and toxicological properties, *Pharmaceutical Chemistry Journal*, **1999**, 33, 232-243.
4. J. Weber, M. Antonietti, A. Thomas, Mesoporous poly (benzimidazole) networks via solvent mediated templating of hard spheres, *Macromolecules*, **2007**, 40, 1299-1304.
5. C. Soula, C. Luu.Duc, L'apport des dérivés du benzimidazole en chimie thérapeutique, *Lyon Pharmaceutique*, **1986**, 37, 297-302.
6. R. Rastogi, S. Sharma, 2-Aminobenzimidazoles in organic syntheses, *Synthesis*, **1983**, 11, 861-882.
7. R.Zou, K.R.Ayres, J.C.Drach, B.Leroy, Synthesis and antiviral evaluation of certain disubstituted benzimidazole ribonucleosides, *Journal of Medicinal Chemistry*, **1996**, 39, 3477-3482.
8. K. S. Gudmundsson, G. A. Freeman, J. C. Drach, L. B. Townsend, Synthesis of fluorosugar analogues of 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole as antivirals with potentially increased glycosidic bond stability, *Journal of Medicinal Chemistry*, **2000**, 43, 2473-2478.
9. Z. Zhu, B. Lippa, J. C. Drach, L. B. Townsend, Design, synthesis, and biological evaluation of tricyclic nucleosides, *Journal of Medicinal Chemistry*, **2000**, 43, 2430-2437.
10. J. R. Hwu, R. Singha, S. C. Hong, Y. H. Chang, A. R. Das, Synthesis of new benzimidazole–coumarin conjugates as anti-hepatitis C virus agents, *Antiviral Research*, **2008**, 77, 157-162.
11. S. Lee, K. Sivakumar, W. S. Shin, F. Xie, Q. Wang, Synthesis and anti-angiogenesis activity of coumarin derivatives, *Bioorganic and Medicinal Chemistry Letters*, **2006**, 16, 4596-4599.

12. J. Neyts, E. D. Clercq, R. Singha, Y. H. Chang, A. R. Das, Structure activity relationship of new antihepatitis C virus Agents, *Journal of Medicinal Chemistry*, **2009**, 52, 1486-1490.
13. J. Velık, V. Baliharova, J. F. Gremmels, S. Bull, J. Lamka, Benzimidazole drugs and modulation of biotransformation enzymes, *Research in Veterinary Science*, **2004**, 76, 95-108.
14. E. B. Yang, Y. N. Zhao, K. Zhang, P. Mack, Daphnetin, one of coumarin derivatives, is a protein kinase inhibitor, *Biochemical and Biophysical Research Communications*, **1999**, 260, 682-685.
15. J. E. Thomas, M. Venugopalan, R. Galvin, Y. Wang, G. M. Bokoch, Inhibition of MG-63 cell proliferation and PDGF-stimulated cellular processes by inhibitors of phosphatidylinositol 3-kinase, *Journal of Cellular Biochemistry*, **1997**, 64, 182-195.
16. D. W. Fry, A. J. Bridges, A. J. Kraker, A. McMichael, M. Nelson, Recent advances in tyrosine kinase inhibitors, *Assoc Cancer Res*, **1995**, 36, 689.
17. R. Pech, R. Böhm, Synthesis of lyzing 2-substituted alkanolphosphoric acid-esters, *Die Pharmazie*, **1984**, 39, 4-13.
18. D. W. Fry, Protein tyrosine kinases structure, substrate specificity, and drug discovery, *Academic Press*, **1996**, 31, 151-160.
19. A. J. Bridges, H. Zhou, Synthesis of [1] benzothieno[3,2-*d*] pyrimidines substituted with electron donating substituents on the benzene ring, *Journal of Heterocyclic Chemistry*, **1997**, 34, 1163-1172.
20. Y. V. Bilokin, M. V. Vasylyev, O. V. Branytska, S. M. Kovalenko, V. P. Chernykh, A novel and expedient approach to new heterocycles containing benzothiophene, benzothieno[2,3-*d*]pyrimidine and coumarin moieties, *Tetrahedron*, **1999**, 55,13757- 13766.
21. D. H. Boschelli, Z. Wu, S. R. Klutchko, H. H. Showalter, J. M. Hamby, Synthesis and tyrosine kinase inhibitory activity of a series of 2-amino-8H-pyrido[2,3-d]pyrimidines, *Journal of Medicinal Chemistry*, **1998**, 41, 4365-4377.
22. S. H. Lee, J. Vora, L. D. Menezes, M. Wiesmann, E. Garrett, Rapid access synthesis of quinoline, chromene, thiochromene benzimidazol, *Bioorganic and Medicinal Chemistry Letters*, **2003**, 5, 2423-2428.
23. L. Mini, Quan, T. Andrew Synthesis of benzimidazole derivatives, *J. Med. Chem*, **1995**, 38, 2938-2945.
24. A. Claud, Bern Hart, M. Pierre, Perreut, Synthesis and characterization of some benzimidazole derivatives using as anti-hypertensive agents, *J. Med. Chem*, **1993**, 36, 3371-3380.
25. J. R. Kumar, J. Jawahar, D. P. Pathak, Synthesis of benzimidazole derivatives as anti-hypertensive agents, *E-Journal of Chemistry*, **2006**, 0973-4945.
26. M. L. Quan, A. T. Chiu, Synthesis of benzimidazole derivatives: as antihypertensive agents, *Bioorg. Med Chem*, **1994**, 4, 2011-2011
27. J. E. Scaly, J. N. Laragh, Synthesis of benzimidazole derivatives: as anti-hypertensive agents, *Bioorg. Med Chem*, **1990**, 1287.