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Research Article

FACILE AND EFFICIENT MICHAEL ADDITION TOWARDS ONE-POT SYNTHESIS OF NOVEL BENZIMIDAZOLE ASSOCIATED CHROMEN-2-ONES

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ABSTRACT

A novel series of various 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2*H*-chromen-2-one and its derivatives (9a-f) have been synthesised via a unique reaction in good to excellent yields from 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylprop-2-en-1-one (7) and 4-methyl-2*H*-chromen-2-ones (8a-f). The study of this synthetic method is extended in different solvents and various bases in order to estimate the better reaction condition in terms of yields of the products.

INTRODUCTION

Compounds having benzimidazole as a structural motif have been widely used in medicinal chemistry and drug development, and researchers are actively seeking new uses and applications of this heterocycle.[1] Benzimidazole containing compounds have numerous medical and biological activities such as antitumor,[2] antibacterial,[3-6] antifungal,[7] antiviral,[8-12] anticonvulsant,[13] antidepressant,[14] analgesic,[15] anti-inflammatory[16] and antidiabetic.[17] The derivatives like thiabendazole (1), cambendazole (2), parbendazole (3), mebendazole (4), albendazole (5) and flubendazole (6) are widely used as anti-helminth drugs to treat people and animals with gastrointestinal worm infections.[18] On the other hand, coumarin and its derivatives are biologically and pharmacologically active compounds with a wide range of properties as antitumor, antimicrobial, anti-HIV, anticoagulant, anti-inflammatory and antioxidant agents.[19,20] Coumarins belong to the flavonoid class of compounds that are mainly isolated from natural plants. In addition, some coumarins are also found in microorganisms like novobiocin, coumermycin A1 and chlorobiocin.[21,22] The Michael reaction is one of the most powerful tools for the formation of carbon-carbon bonds in organic synthesis.[23] These are recognized as versatile synthetic building blocks which can be either transformed into biologically active compounds,[24] or readily converted into other functionalities.[25]

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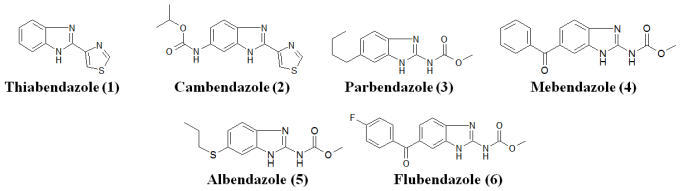


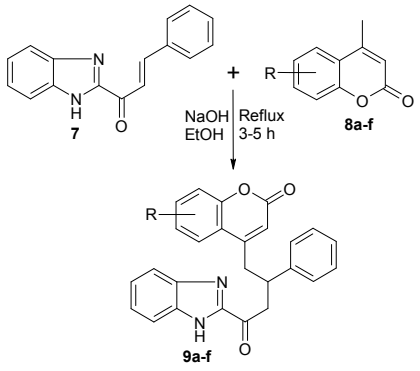
Scientific literature is more and more focused on a combination of different pharmacophores in a single molecular framework to generate innovative bifunctional drugs as one of the most challenging and attractive topics for the constructing of novel bioactive molecules. Thus, the linkage between benzimidazol and chromone become a useful connection and may lead to new compounds having higher activity in the treatment various microbial infections.

RESULTS AND DISCUSSION

Based on all above considerations and extension of our studies on the development of novel heterocyclics, we turned our attention to investigate the scope and generality of this method by carrying out the synthesis of 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2*H*-chromen-2-one and its derivatives **(9a-f)** as resulted novel Michael adducts in good yields (77-85%) by clubbing the raw material, 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylprop-2-en-1-one **(7)** (prepared in the same way as described in the literature[26]) with different 4-methyl-2*H*-chromen-2-ones **(8a-f)** by employing sodium hydroxide as base in the presence of absolute ethyl alcohol as solvent under reflux in a water bath with constant stirring for 3-5 h through Michael addition in a single step as illustrated in scheme 1.

To demonstrate the generality and scope of this method, the reaction was carried out with various substituted and structurally diverse chromones and it was found that in all the

cases high yields of the products are formed. As per the results (Table 1), this reaction efficiently promoted using chromones containing EWGs with high yields rather than with EDGs. All the newly synthesized compounds have been characterized by different spectroscopic techniques like IR, ^{1}H NMR, mass and elemental analysis which confirmed the chemical structures.



Scheme 1 Synthesis of 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2*H*-chromen-2-ones (9a-f) as novel Michael adducts.

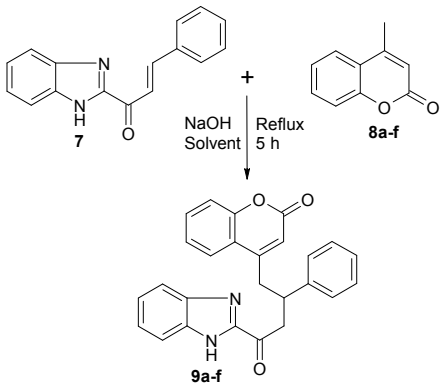
Table 2 Study of the Michael reaction under different bases in the presence of EtOH

Entry	Hybrid	Base	Time (h)	Yield (%)[a]
1	9a	NH_3	5.0	18
2	9a	NaOH	5.0	85
3	9a	KOH	5.0	87
4	9a	EtONa	5.0	90
5	9a	LDA	5.0	93
6	9a	$NaNH_2$	5.0	97

[a] Isolated yield after purification

This novel Michael addition of 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylprop-2-en-1-one (7) with 4-methyl-2*H*-chromen-2-one (8a) to offer the corresponding 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2*H*-chromen-2-ones (9a) is also carried out independently in the presence of several bases such as NH_3, NaOH, KOH, LDA and $NaNH_2$ in ethanol under reflux with uniform stirring for 5 h in order to select the efficient base. The product 9a was obtained in lowest yield (Table 2, entry 1) with using NH_3 (weak base) as base for at reflux temperature 5 h. However, the same product 9a was achieved in 85%, 87%, 90% and 93% of yield by employing bases like NaOH, KOH (moderate bases), EtONa and LDA (strong bases) under similar conditions. The highest yield (97 %) of the product 9a was obtained in the presence of $NaNH_2$ (strong base) as base and thus concluded that the conversion disclosed excellent performance in terms of yield and was selected as model reaction.

We then tested this transformation in different alcohols like methanol, ethanol, isoproponol, *t*-butanol, *n*-hexanol and cyclohexanol in the presence of NaOH as base at reflux temperature for 5 h and the desired product **9a** was formed in different yields in the range of 78% - 95% with a degree of variation. As per the results reported in Table 3, by changing solvent from methanol to *t*-butanol, the reaction exhibited remarkable improvement in the yield from 78 % to 95 %, where as the yield was reduced to 80 % in *n*-butanol. Highest yield (95%) of **9a** was obtained in *t*-Butanol. Finally, after extensive screening, we found that the optimized best yield was furnished by using $NaNH_2$ as base and *t*-butanol as solvent.



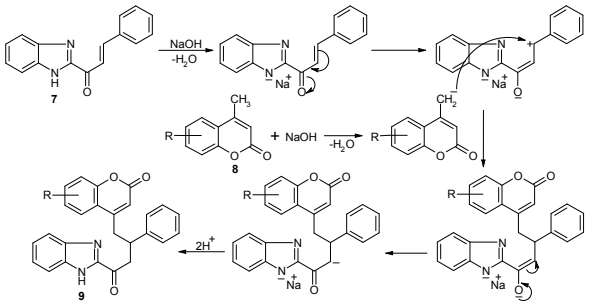
Scheme 3 Study of the solvent effect on the formation of different Michael adduct 9a-f

Table 3 The study of the Michael reaction under different solvents in the presence of NaOH

Entry	Hybrid	Solvent	Time (h)	Yield (%)[a]
1	9a	Methanol	5.0	78
2	9a	Ethanol	5.0	89
3	9a	Isopropanol	5.0	90
4	9a	*t*-Butanol	5.0	95
5	9a	*n*-hexanol	5.0	80
6	9a	cyclohexanol	5.0	82

[a] Isolated yield after purification

A suitable mechanism proposed for the preparation of novel 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl) -2*H*-chromen-2-ones **(9a-f)** from the reaction of 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylprop-2-en-1-one **(7)** with 4-methyl-2*H*-chromen-2-one **(8a)** is shown in scheme 4. This mechanism is assumed to be similar as proposed in various classical and modern Michael reactions.



Scheme 4 Possible mechanism of the novel Michael addition

Experimental

All Reagents and solvents were purchased and used without any further purification. Melting points were determined in capillary tubes on a Fisher-Johns melting point apparatus and are uncorrected. The progress of the reaction and purity of the compounds have been monitored by TLC using analytical silica gel plates (Merck 60 F250). ^{1}H NMR spectra were acquired on Varian 300 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer BX series FTIR 5000 spectrometer using KBr pellet. Mass spectra were obtained on a VG micro mass 7070H spectrometer operating at 70 eV.

Synthesis of 4-(4-(1H-benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2H-chromen-2-ones (9a-f)

An amount of 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylprop-2-en-1-one **(7)** (0.01 mol) and 4-methyl-2*H*-chromen-2-ones **(8a-f)** (0.01 mol) was dissolved in 10 ml of absolute ethanol by adding NaOH (0.01 mol). The reaction mixture was refluxed for 3-5 h on a water bath with constant stirring. After

completion of the reaction (monitored by the TLC), the mixture was cooled, poured onto a mixture of ice and water and neutralized with dilute HCl. Thus, the formed precipitate was filtered, washed with distilled water. The resulting solid was recrystallized from ethylacetate to 4-(4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2*H*-chromen-2-ones (9a-f).

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2H-chromene-2-one (9a)

IR (KBr), υ, cm^{-1}: 3212 (N-H), 3024 (C-H, Ar), 2974 (C-H, CH_2), 1740 (C=O), 1710 (C=O), 1645 (C=N), 1610 (C=C, Ar), 1158 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.36 (m, 1H, CH), 3.18 (s, 2H, CH_2), 3.25 (t, 2H, J = 5.4 Hz, CH_2), 5.25 (s, 1H, CH), 7.25-7.62 (m, 13H, Ar-H), 11.14 (s, 1H, NH), MS, *m/z*: 408 (M^+). Anal. Calcd for $C_{26}H_{20}N_2O_3$. C 76.45, H 4.94, N 6.86, O 11.75, Found C 75.69, H 4.93, N 6.84, O 11.71.

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-2-oxo--2H-chromene-3-carbonitrile (9b)

IR (KBr), υ, cm^{-1}: 3223 (N-H), 3036 (C-H, Ar), 2970 (C-H, CH_2), 1737 (C=O), 1713 (C=O), 1652 (C=N), 1623 (C=C, Ar), 1152 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.33 (m, 1H, CH), 3.20 (t, 2H, J = 5.4 Hz, CH_2), 3.27 (s, 2H, CH_2), 7.29-7.58 (m, 13H, Ar-H), 11.10 (s, 1H, NH), MS, *m/z*: 433 (M^+). Anal. Calcd for $C_{27}H_{19}N_3O_3$. C 74.81, H 4.42, N 9.69, O 11.07, Found C 73.58, H 4.41, N 9.67, O 11.04.

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-6-hydroxy-2H-chromene-2-one (9c)

IR (KBr), υ, cm^{-1}: 3238 (N-H), 3225 O-H), 3042 (C-H, Ar), 2956 (C-H, CH_2), 1733 (C=O), 1718 (C=O), 1665 (C=N), 1632 (C=C, Ar), 1158 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.31 (m, 1H, CH), 3.23 (t, 2H, J = 5.4 Hz, CH_2), 3.31 (s, 2H, CH_2), 5.29 (s, 1H, CH), 7.25-7.61 (m, 9H, Ar-H), 7.36 (d, 1H, J = 7.5 Hz, Ar-H), 7.39 (d, 1H, J = 7.5 Hz, Ar-H), 7.45 (s, 1H, Ar-H), 10.48 (s, 1H, OH), 11.13 (s, 1H, NH), MS, *m/z*: 424 (M^+). Anal. Calcd for $C_{26}H_{20}N_2O_4$. C 73.57, H 4.75, N 6.60, O 15.08, Found C 72.69, H 4.74, N 6.59, O 14.99.

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-7-hydroxy-2H-chromene-2-one (9d)

IR (KBr), υ, cm^{-1}: 3255 (N-H), 3218 (O-H), 3048 (C-H, Ar), 2962 (C-H, CH_2), 1730 (C=O), 1720 (C=O), 1671 (C=N), 1639 (C=C, Ar), 1166 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.33 (m, 1H, CH), 3.18 (t, 2H, J = 5.4 Hz, CH_2), 3.35 (s, 2H, CH_2), 5.20 (s, 1H, CH), 7.30-7.66 (m, 9H, Ar-H), 7.39 (d, 1H, J = 7.3 Hz, Ar-H), 7.42 (d, 1H, J = 7.3 Hz, Ar-H), 7.47 (s, 1H, Ar-H), 10.52 (s, 1H, OH), 11.22 (s, 1H, NH), MS, *m/z*: 424 (M^+). Anal. Calcd for $C_{26}H_{20}N_2O_4$. C 73.57, H 4.75, N 6.60, O 15.08, Found C 72.69, H 4.74, N 6.59, O 14.99.

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-7-hydroxy-2-oxo-2H-chromene-3-carbonitrile (9e)

IR (KBr), υ, cm^{-1}: 3248 (N-H), 3230 (O-H), 3055 (C-H, Ar), 2968 (C-H, CH_2), 1722 (C=O), 1717 (C=O), 1662 (C=N), 1644 (C=C, Ar), 1152 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.39 (m, 1H, CH), 3.15 (t, 2H, J = 5.4 Hz, CH_2), 3.37 (s, 2H, CH_2), 7.35-7.62 (m, 9H, Ar-H), 7.41 (d, 1H, J = 7.2 Hz, Ar-H), 7.49 (d, 1H, J = 7.2 Hz, Ar-H), 7.52 (s, 1H, Ar-H), 10.59 (s, 1H, OH), 11.28 (s, 1H, NH), MS, *m/z*: 449 (M^+). Anal. Calcd for $C_{27}H_{19}N_3O_4$. C 72.15, H 4.26, N 9.35, O 14.24, Found C 71.56, H 4.25, N 9.34, O 14.20.

4-(4-(1H-Benzo[d]imidazol-2-yl)-4-oxo-2-phenylbutyl)-3-chloro-7-hydroxy-2-oxo-2H-chromene-2-one (9f)

IR (KBr), υ, cm^{-1}: 3235 (N-H), 3220 (O-H), 3043 (C-H, Ar), 2958 (C-H, CH_2), 1725 (C=O), 1715 (C=O), 1672 (C=N), 1636 (C=C, Ar), 1148 (C-O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.32 (m, 1H, CH), 3.19 (t, 2H, J = 5.4 Hz, CH_2), 3.42 (s, 2H, CH_2), 7.31-7.58 (m, 9H, Ar-H), 7.43 (d, 1H, J = 7.0 Hz, Ar-H), 7.45 (d, 1H, J = 7.0 Hz, Ar-H), 7.55 (s, 1H, Ar-H), 10.63 (s, 1H, OH), 11.23 (s, 1H, NH), MS, *m/z*: 458 (M^+). Anal. Calcd for $C_{26}H_{19}ClN_2O_4$. C 68.05, H 4.17, N Cl 7.73, N 6.10, O 13.95, Found C 67.58, H 4.16, N Cl 7.71, N 6.09, O 13.68.

References

1. M. Wang, X. Han, Z. Zhou, *Expert Opin. Ther. Pat*. 2015, *25*, 595-612.
2. K. J. Soderlind, B. Gorodetsky, A. K. Singh, N. R. Bachur, G. G. Miller, J. W. Lown, *Anticancer Drug. Des*. 1999, *14*, 19-36.
3. K. Kumar, D. Awasthi, S. Y. Lee, J. E. Cummings, S. E. Knudson, R. A. Slayden, I. Ojima, *Bioorg. Med. Chem*. 2013, *21*, 3318-3326.
4. E. Mentese, H. Bektas, S. Ulker, O. Bekircan, B. Kahveci, *J. Enzyme Inhib. Med. Chem*. 2014, *29*, 64-68.
5. K. J. Veli, V. Baliharova, J. Fink-Gremmels, S. *Bull, J.* Lamka, L. Skalova, *Res. Vet. Sci*. 2004, *76*, 95-108.
6. R. Janupally, V. U. Jeankumar, K. A. Bobesh, V. Soni, P. B. Devi, V. K. Pulla, P. Suryadevara, K. S. Chennubhotla, P. Kulkarni, P. Yogeeswari, *Bioorg. Med. Chem*. 2014, *22*, 5970-5987.
7. Y. Ke, X. Zhi, X. Yu, G. Ding, C. Yang, H. Xu, *Comb. Chem. High Throughput Screen* 2014, *17*, 89-95.
8. M. Tonelli, G. Paglietti, V. Boido, F. Sparatore, F. Marongiu, E. Marongiu, P. La Colla, R. Loddo, *Chem. Biodivers*. 2008, *5*, 2386-2401.
9. G. Vitale, P. Corona, M. Loriga, A. Carta, G. Paglietti, C. Ibba, G. Giliberti, R. Loddo, E. Marongiu, P. Colla, *Med. Chem*. 2010, *6*, 70-78.
10. M. Tonelli, M. Simone, B. Tasso, F. Novelli, V. Boido, F. Sparatore, G. Paglietti, S. Pricl, G. Giliberti, S. Blois, *Bioorg. Med. Chem*. 2010, *18*, 2937-2953.
11. G. Vitale, P. Corona, M. Loriga, A. Carta, G. Paglietti, G. Giliberti, G. Sanna, P. Farci, M. E. Marongiu, P. Colla, *Eur. J. Med. Chem*. 2012, *53*, 83-97.
12. M. Tonelli, F. Novelli, B. Tasso, I. Vazzana, A. Sparatore, V. Boido, F. Sparatore, P. Colla, G. Sanna, G. Giliberti, *Bioorg. Med. Chem*. 2014, *22*, 4893-4909.
13. R. V. Shingalapur, K. M. Hosamani, R. S. Keri, M. H. Hugar, *Eur. J. Med. Chem*. 2010, *45*, 1753-1759.
14. N. Siddiqui, S. Andalip Bawa, R. Ali, O. Afzal, M. J. Akhtar, B. Azad, R. Kumar, *J. Pharm. Bioallied Sci*. 2011, *3*, 194-212.
15. P. A. Datar, S. A. Limaye, *Med. Chem*. 2015, *14*, 35-46.
16. K. C. S. Achar, K. M. Hosamani, H. R. Seetharamareddy, *Eur. J. Med Chem*. 2010, *45*, 2048-2054.
17. Y. Bansal, O. Silakari, *Bioorg. Med. Chem*. 2012, *20*, 6208-6236.
18. H. S. Cho, P. F. Lopes, (2011): United States Patent NO. 20130090296.

19. I. Kostova, Curr. *Med. Chem*. 2005, *5*, 29-46.
20. A. A. Al-Amiery, A. Kadhum, A. Mohamad, *Molecules* 2012, *17*, 5713-5723.
21. S. S. Bahekar, D. B. Shinde, Tetrahedron Lett. 2004, *45*, 7999-8001.
22. B. G. Lake, *Food Chem. Toxicol*. 1999, *37*, 423-453.
23. S. Sulzer-Moss, A. Alexakis, Chem. Commun. 2007, *30*, 3123-3135.
24. C. Czekelius, E. M. Carreira, Angew. Chem. Int. Ed. 2005, *44*, 612-615.
25. R. Ballini, M. Petrini, Tetrahedron 2004, *60*, 1017-1047.
26. K. Ravinder Reddy, V. Malla Reddy, B. Srinivas, Inter. *J. Pharma. Sci. Drug* Res. 2014, *6,* 278-282.

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